Lymphatic mapping and sentinel node biopsy in breast cancer

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Findings by SBU Alert

Breast cancer surgery always includes an investigation to determine whether cancer has spread to the axillary lymph nodes. In addition to removing the tumor itself, traditional treatment also includes removing several of the axially lymph nodes, for both diagnostic and therapeutic reasons. The intervention carries a substantial risk for complications, eg, edema and limitations in the range of motion. By identifying and investigating the first lymph node (sentinel node) into which the tumor drains, it is possible to avoid unnecessary removal of lymph nodes. The sentinel node is analyzed for the presence of cancer. If this node is cancer free, it is assumed that cancer has not spread to the other lymph nodes, and they can be saved. The method can help reduce suffering in approximately 60 per cent of all breast cancer patients.

A decisive issue concerns the potential for this method to eliminate the possibility that cancer has spread to the other lymph nodes. To date, the method has been tested in several small, and two large, nonrandomized studies. The results from these studies show that the sentinel lymph node could be identified in 87 to 98 per cent of the cases. Approximately 10 per cent of the diagnostic results were false negative (ie, wrongly indicated no tumor).

According to the findings of SBU Alert, moderate* scientific knowledge is available concerning the value of the method as a prognostic instrument. Poor* scientific knowledge is available concerning how the method benefits patients, ie, how the method affects treatment outcomes and quality of life. These aspects, and the cost-effectiveness of the method need further assessment.

Greater knowledge is needed before the method can be accepted as standard medical practice. Results from ongoing studies should first become available, or the method should be addressed within the framework of an assessment study.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

In breastcancer the status of the axillary node basin, ie, presence of tumor cells in the axillary lymph node, is the single most important prognostic factor and important clinical decisions are based on it. The possible spread of cancer is determined by analyzing the lymph nodes removed from the armpit (axillary dissection) in conjunction with breast cancer surgery. Axillary dissection is also therapeutic since it lowers the rate of axillary recurrences and may also affect the overall survival. Axillary clearance is however associated with a substantial risk for later complications, including seroma formation, lymphedema, neuropathy of the arm with numbness, stiffness, weakness and pain.

The Sentinel Node method is based on the theory that the first lymph node that drains the tumor is also the first node to be affected by the spreading tumor. The hypothesis is, if the sentinel node is negative , ie, cancer free, the cancer has not spread to other axillary lymph nodes. In breast cancer patients with a negative sentinel node, excision of the lymph nodes could thus be avoided.

The method involves injecting a radioactive isotop peritumorally or subdermally above the tumor. By lymphscintigraphy its path to the first lymph node (sc sentinel node) is mapped. The lymph scintigraphy is performed 4–26 hours prior to surgery. During the operation a blue dye can be injected in the breast tumor to help identify the first node. The identification of the sentinel node during the operation can be done using a dye and with a portable gamma probe which registers radioactivity in the node. In the Swedish centers where this research is carried out, both methods are used in parallel.

The first lymphatic node (which may actually involve one to three nodes) is removed and analyzed to determine if the tumor has spread. The node can be identified in more than 90 per cent of the cases. At the present stage of development, the armpit is excised in the usual way to determine if the first lymph node correctly reflects the status of the other nodes.

In addition to breast cancer, the method has also been tested on malignant melanoma and penile cancer. It should also be applicable to other types of cancer.

Target group

The rate of new cases of primary breast cancer is approximately 104 per 100 000 women (Cancer Registry, 1996), which corresponds to approximately 5 000 new cases per year in Sweden. Patients with metastases in the axillary lymph nodes, found prior to surgery or during the breast operation, have no benefit of this method. Approximately 60 per cent (3 000) of all breast cancers have no metastases in the axillary lymph nodes and may benefit from this new method, since axillary clearance thus can be avoided**.**

Relation to other technology

Other methods besides clinical examination that have been used preoperatively to determine the possible spread of a tumor to the armpit include, eg, computerized tomography, ultrasound, and positron emission tomography (PET). These methods have been less effective than lymphatic mapping in confirming the presence of cancer in the lymph nodes.

Patient benefits

The method has been tested in a number of small case studies including between 30 and 160 patients [1,3,5,6,8,9]. Two larger non-randomized studies has been completed, one multicenter trial including 443 patients and one including 492 patients [4,7]. In most of the studies a combination of the blue dye and the isotop method were used. In some studies only one of the techniques was evaluated.

The first lymph node was localized in 87 to 98 per cent of the cases [1,4–9]. The studies have also shown that the method correctly predicted the status of the axilla in 90 to 100 per cent [1,3–9]. The false negative rate, ie, the percentage of false indications on being cancer free, was around 11.0 per cent [4,7].

Preliminary results from a Swedish pilot study including 75 patients indicate that the first lymph node could be identified in more than 92 per cent of the cases, and that the possibility to predict the status of

the axilla was more than 95 per cent. The false negative rate here was also 11 per cent [2]. These results, however, reflect the initial learning phase of the method, and are expected to improve.

Another potential benefit of this method is the possibility to analyse the first lymph node for micro metastases which leads to a better staging of the tumor.

Complications and side effects

The examination itself is not associated with risks for side effects or complications, apart from what follows from the operation itself.

There is however a risk for false negative results, ie, that the first lymph node is tumor free, although a spread of tumor actually has occurred. The false negative rate is the number of cases with a negative first lymph node and the total number of cases with lymph node metastases. This has in the small case studies been reported to vary between 0 to 11 per cent [1,3,5,6,8,9]. In the two larger studies it was around 11 per cent [4,7]. A national multicenter trial in Sweden including 500 patients is going on. A preliminary analysis of the first 450 patients indicate a false negative rate of approximately 8 per cent.

A complicating factor in lymphatic mapping involves the need to have access to histopathological analysis of the first lymph node during the operation. Results of the analysis are necessary to determine whether or not to remove the lymph nodes of the armpit. Without an accurate analysis, patients will need to be reoperated if later analysis reveals that the tumor has spread to the other lymph nodes.

Costs and cost-effectiveness

Portable lymphatic mapping equipment costs approximately 200 000 SEK plus VAT (1998). When the sentinel lymph node is assessed according to the method described here, the length of time needed for cancer surgery is somewhat longer, but is otherwise not associated with any additional costs.

If the method proves successful, tumor-negative patients will be subjected to only a minor surgical procedure. This may lead to a shorter length of stay and provide an opportunity for the operation to be carried out in day surgery. Fewer complications will also reduce the need for care. However, it is too early to estimate potential cost reductions. Nor is it possible to estimate the cost-effectiveness of the method.

Structure and organization of health services

In principle, the method can be used in any facility that offers surgery for breast cancer. Lymphatic mapping is performed the same day or the day prior to surgery in a hospital having a radioisotope department. Surgery may thereafter take place in another hospital. No new requirements have been established concerning competence or staff composition. Some training is required to master the technique.

Ethical aspects

An issue is what can be considered as an acceptable risk, ie, how many false negative results can be accepted so that the majority of patients with true negative results do not have to undergo excision of axillary lymph nodes.

In studies of the characteristics of the sentinel node biopsy and to determine the prognostic qualities of the method, the patients may function as their own controls. A traditional lymph node clearance has been carried out, whereafter status of the sentinel node has been compared to status of the rest of the lymph nodes for each patient. To evaluate the net benefit/harm for the patients and the cost-effectiveness of the method, randomized control trials are needed.

Diffusion in Sweden

The method was first tested in 1997/1998 at Huddinge Hospital and Västerås Hospital, but is currently used at most of the larger hospitals in Sweden. Patients from all hospitals that use the method are included in studies.

Current evaluation research

A pilot study including 75 patients at Västerås Hospital, Huddinge Hospital and Örebro Hospital is finished and evaluated. The Swedish Society on Breast Surgery has initiated a multicenter trial. The study includes 500 patients whereof 450 patients from 15 centers are already included. A study that examines the importance of training for the safety of the method is also being assessed. This study has included 498 patients. Ongoing studies will be assessed during the autumn of 2000.

A cohort study is starting during the autumn of 2000 to investigate the rate of recurrence in patients with negative test results from the sentinel lymph node following biopsy alone. The study will include 1 500 patients.

Expert

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