Implementing Lymphatic Mapping With Sentinel Node Biopsy in The Management of Patients with Breast Cancer

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Lymphatic mapping with sentinel node biopsy is a minimally invasive procedure that has the potential to provide accurate staging information in patients with breast cancer. Axillary node dissection can thus be reserved for patients with involved nodes. The best results are obtained with a multidisciplinary team approach. The author recounts his experience with the introduction of this technique at his institution and share his knowledge gained by helping others to do so.

KEYWORDS
Breast neoplasms, sentinel lymph node biopsy, review, neoplasm staging, axillary lymph nodes.

INTRODUCTION

The past decade has brought major advances in the knowledge about breast cancer. The understanding of the underlying mechanisms of the disease has been increased by molecular biology and this field appears on the brink of becoming part of routine clinical management. The ability to diagnose the disease has been refined. New drugs have been introduced and really improve survival. If one wonders what the most significant recent advance is in the surgical management, then the author submits that lymphatic mapping is it, although he admits maybe being somewhat biased.

Lymphatic mapping, also known as sentinel node biopsy, was developed for melanoma at the John Wayne Cancer Center in Santa Monica and was first published by Morton in 1992. The principles of the method can be explained in a few sentences. Extracellular fluid enters lymph vessels for transportation back to the blood pool. For purification, the lymph fluid passes through a series of lymph nodes, organized in clusters in specific regions. The sentinel lymph node is the lymph nodes to which the lymph fluid that originates in a primary tumor drains directly through a lymphatic duct. The exfoliated malignant cells that the fluid may contain are filtered out in the lymph node and may reside there. They may proliferate and pass tumor cells on to directly at risk to receive metastasis cells and the first one to contain metastasis.

The sentinel node can be visualized using lymphoscintigraphy. A radioactive tracer is administered in the breast and travels through a lymph vessel to the sentinel node. The node can be depicted with a gamma camera. The surgeon can find this node by identifying its radioactivity with a small gamma ray detection probe or by tracing a blue dye administered in the breast instead of receiving the entire contents of the axilla, the pathologist receives one or at the most a few nodes. Such a node can be examined with routine haematoxylin and using sensitive immunohistochemistry staining techniques. Patients with early breast cancer are candidates for sentinel node biopsy.

Before lymphatic mapping was introduced, surgeons used to remove all the axillary nodes routinely. Lymphatic mapping allows them to restrict axillary clearance to patients with proven lymph node metastases. The others undergo just sentinel node biopsy but are spared an axillary clearance that they do not need because they do not have metastases there. The

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tumor-status of the sentinel node dictates whether or not axillary node dissection needs to follow.

At the Netherlands Cancer Institute, the potential of lymphatic mapping was quickly perceived. The author went to Santa Monica in 1993 to learn how to do the procedure and the technique was introduced in Europe. A multidisciplinary team was formed and lymphatic developed into one of the topics of interest. Once the team felt comfortable with the technique, others were taught how to do it. To the is end, courses were organized, educational materials were written, teaching programs abroad were supported and numerous guests came to the institution eager to learn the procedure. This article was written to help doctors caring for breast cancer patients in Indonesia in their efforts to implement lymphatic mapping at their institutions.

SPECIMEN STUDY

A number of studies were performed in addition to the educational efforts. Our first study demonstrates how one can evolve into the other. Because lymphatic mapping was based on a hypothesis that breast cancer spreads in a step-wise fashion through the lymphatic system, we felt that this theory needed to be proven before the procedure could be carried out in patients. A study was initiated in which patent blue dye was injected into the breast tumor when the patient was on the operating table for mastectomy. While the tracer was taken up by the lymphatic system and flowed through a lymphatic duct to the regional nodes, the mastectomy was done as always with in-continuity axillary node dissection. The tissue specimen was taken to the pathology laboratory and there it was dissected. The first thing we did was to establish that we were successful at staining the tumor blue. Then, the blue stained lymphatic channel that emerged from the cancer was identified and carefully dissected all the way until it drained into a blue stained sentinel lymph node. The blue node was taken out and examined separately by the pathologist. The other nodes were examined very carefully as well.

This was done in thirty patients. The blue node was shown to be involved in all ten patients in whom metastases were found in the axilla. In six patients, the sentinel node was the only node involved. This was our way of validating the concept of step wise spread of breast cancer through the lymphatic system and the outcome gave us the confidence that this technique should be pursued further.

In hindsight, this was also a good way to gain some experience in dissecting lymphatic channels. The blue dye was injected in vivo, but the actual dissection of the lymphatic channels are very fragile and easily damaged. Practicing on mastectomy specimens is an attractive and harmless way to get started. This approach enables the surgeon to dissect in an unhurried fashion without pressure from the operating room schedule. The specimen is easily accessible from all angles, providing the best possible exposure one could wish. This approach will give the surgeon a head start when the procedure is taken to the operating room.

LYMPHOSCINTIGRAPHY AND INTRA-OPERATIVE APPROACH

Lymphoscintigraphy can visualize the lymph drainage pattern from the breast. Albumin colloid labeled with technetium-99m can be administered in the tumor area. This agent enters the lymphatic vessels and travels to the sentinel node where it is taken up by the macrophages. This physiologic process can be captured on lymphoscintigrams. This elegant imaging technique is now becoming controversial. More than half of the surgeons in the USA do not routinely order lymphoscintography before the operation. These surgeons rely on the tools that they can use during the operation and feel that these are all they need. Our nuclear medicine physicians studied the relevance of lymphoscintigraphy. They showed that lymphoscintigraphy helps the surgeon to find all sentinel nodes and helps to prevent unnecessary removal of second-tier nodes (table 1). Lymphoscintigraphy provides the surgeon with a road map. In contrast to the situation in the USA, every surgeon in the Netherlands always orders lymphoscintigraphy. Lymphoscintigraphy visualizes a sentinel node in 95% of the patients.

There are two surgical approaches to find a sentinel node: instrument-guided surgery and visually guided surgery. The first approach involves a gamma ray detection probe to direct the surgeon to the radioactive sentinel node. The second approach makes use of a vital blue dye administered in the tumor area. This dye is also taken up by the lymphatic system. The surgeon can identify the blue-stained lymphatic vessel in the axilla and dissect in until it drains into a blue-stained sentinel node. Only blue nodes that receive drainage directly from the cancer are considered to be sentinel nodes, others need not be removed.

Some surgeons use only one of the two tracers with good results. At the Netherlands Cancer Institute, the

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three techniques are always combined and it was found that 50% of the sentinel nodes are both radioactive and blue, 30% are only radioactive and 20% are only blue. It appears that the comprehensive approach offers the best chance of finding all sentinel nodes while avoiding the unnecessary removal of secondary nodes.

LEARNING PHASE

One of the first things that need to be done before initiating a lymphatic mapping program is to form a team involving a nuclear medicine physician, a surgeon, a pathologist and, probably, a radiologist. The team needs a leader. There must be one enthusiastic local champion who organizes the team, and who will take care of the nitty gritty. This usually is the surgeon, because the surgeon is the pivot on whom the various aspects hinge.

For a learning phase, the surgeon will do sentinel node biopsy followed by confirmatory complete axillary node dissection. At The Netherlands Cancer Institute, the learning phase consisted of 81 patients for three surgeons, two of whom had experience with the procedure in melanoma patients. They could identify the sentinel node in 72 of the patients (89%). This has improved to 98% nowadays. These numbers suggest a fairly long learning phase.

The question of how many cases a learning phase should consist has often been posed. Since we did not know the answer, a literature review was performed and befriended experts were asked for their opinion. We ended up with an average of 25 procedures and a range from ten to 80. However, none of the recommendations that were obtained was based on more than a hunch.

A mathematical exercise was performed in order to find a statistically sound answer. The purpose was to calculate how many procedures needed to be carried out in order to determine that a surgeon can identify the node in 95% of the patients with a false negative rate of not more than 5%. Both elements play a role in the learning phase. False negative means that there is tumor in the axilla but the node that is removed is found to be disease-free. Our calculation revealed that in order to determine with 95% certainty that these reasonable aims are met, a surgeon with an average practice would need to do 750 procedures.

This calculation does not mean that 750 cases are required to learn the technique. There may be surgeons who can collect the desired skill after having completed learning phase of twenty-five patients, but it takes 750 cases to prove that they have obtained the required skills. Obviously, 750 is not a realistic number to pursue. Furthermore, this number is calculated for the surgeon's learning phase. The nuclear medicine physician and the pathologist are other links in the chain. The nuclear medicine people have their own learning phase. In the beginning, our nuclear medicine physicians could visualize a sentinel node in merely 78% of the patients. This has improved to 95% later on. A surgeon, no matter how skilled, will never find 95% of the sentinel nodes if not backed by a competent nuclear medicine physician. And, a surgeon will never keep the false negative rate down to 5% if not backed by a diligent pathologist. The paradox of the learning phase is that a good pathologist who scrutinizes the non-sentinel nodes with step-sections and immunohistochemistry will make a surgeon look worse, and a less meticulous pathologist will make a surgeon look better than he or she actually is. One can only conclude that a statistically sound learning phase is not attainable in clinical practice and that a clinically practical learning phase lacks the desired statistical significance.

In the USA and in the Netherlands, introduction of lymphatic mapping occurred in a less than organized fashion and without much thought. Surgeons would not commit themselves to a long learning phase, being pressured by their patients and knowing that their colleagues in a neighboring hospital had already adopted lymphatic mapping as their standard of care. As a result, many surgeons abandoned the confirmatory axillary node dissection after a learning phase of less than ten cases. The New Start program requires the surgeons accompanied by their nuclear medicine physicians to attend a teaching course first. Then, they do five cases in their own institution, supervised by a designated national expert. This is followed by a validation phase of 25 cases with confirmatory node dissection. In this learning phase, a sentinel node must be identified in 90% of the patients and the false negative rate may not exceed 10%. Although these numbers will not satisfy a statistician, this approach seems to be a reasonable compromise.

OMITTING CONFIRMATORY AXILLARY NODE DISSECTION

After a successful learning period, the surgeon will abandon the routine axillary node dissection and reserve this larger procedure for sentinel node-positive patients. It makes sense to keep recording the data associated with lymphatic mapping, like the scan
findings, the probe readings, the operative findings and the pathology reports. It can be very informative to analyze the patients with unexpected findings, the procedures in which the sentinel node was not identified and the false negative cases. The author has been blessed – or cursed – with young investigators who take a particular interest in his failures. They have analyzed the false negative cases, they identified mistakes and their findings have prompted changes in the protocol. \(^{11, 12}\) An example was the finding of one of the causes of false negative procedures. In some patients, a hot and blue node was found to be tumor-free on frozen section examination. The surgeon decided that patient could be spared axillary node dissection and started to close the deep fatty tissue in the axilla. By chance, a rock-hard node was encountered that had not been palpable through the intact skin before the operation. The node was clearly tumor-positive although it was neither blue nor radioactive. This means that it was not a sentinel node according to the definition. The most likely explanation is that the lymph fluid originally went to this suspicious node. At a certain point in time, the increasing tumor mass blocked the flow into the node and the lymph was diverted to another lymph node. This "neo"-sentinel node was not yet tumor-positive at the time of the operation. The radioactivity and the blue dye traveled to the neo-sentinel node and this node was removed as if it were the only true sentinel node. The result was a false negative case.

Of course, the suspicious node was removed and sent for frozen sections. Axillary clearance was performed in the same session. A few of such patients were encountered and these left us with the uneasy feeling that an axillary recurrence was avoided by sheer luck each time. A review of the literature revealed that Haagensen had already described this phenomenon.\(^{13}\) He injected a dye called Direct Sky Blue in the breast and observed that grossly involved nodes did not stain, whereas adjacent uninvolved nodes did stain.

To solve the problem, two changes were made in the protocol. Intra-operative palpation of the axilla was introduced to diminish the risk of leaving behind involved nodes in the presence of a false-negative sentinel node. More involved nodes that failed to pick up the tracers have indeed been identified since. Also, preoperative ultrasound of the axilla was introduced. Ultrasound identifies non-palpable nodes that are largely replaced by metastatic disease. Fine needle aspiration cytology confirms the presence of tumor in such nodes. Of all patients with involved nodes, 21% are now identified through ultrasound. These are the nodes with massive tumor invasion that will fail to pick up the tracer fluid and these nodes are bound to cause recurrences later on.

So, the radiologist has been welcomed as new members of the team. Ultrasonography is now a standard element of the sentinel node procedure at our institution. The value of intra-operative palpation and ultrasound are lessons that we were able to learn because we document our findings and we analyze our failures.

**CONCLUDING REMARKS**

The trend for more conserving local-regional treatment has been going on for many years. It was to be expected that surgeons would investigate whether axillary node dissection can be omitted safely in selected patients. Lymphatic mapping with sentinel node biopsy is a logical step.

The current practice of routine axillary node dissection serves four purposes: it assures local-regional control, it improves survival, and it provides important information for staging and for prognosis. Sentinel node biopsy can provide even more extensive staging information through detailed evaluation of sentinel nodes and may also include sentinel nodes outside the axilla. Given the considerable morbidity of axillary node dissection, this less invasive approach is attractive. The results with technique are favorable. The sentinel node can be identified in over 95% of the patients. A literature review of studies following patients who did not undergo axillary node dissection because their sentinel node was free of disease showed that the recurrence rate in the axilla was 0.4%.\(^{14}\) Based on these findings, one is led to conclude that axillary node dissection should be reserved for patients who indeed have lymph node metastases. A great number of breast cancer patients can now be spared an unnecessary axillary node dissection. And still, local-regional control remains unaffected and survival probably too. The same important information for staging and prognosis remains available. A substantial reduction in patient morbidity and medical expenses is the result. These observations appear to justify the implementation of lymphatic mapping in ever more countries.

Still, a few words of caution are appropriate. The author has seen a lot of surgeons do a lot of sentinel node biopsies and has come to realize that nor every surgeon can do this. There are surgeons who never will learn to do the procedure well. This does not
implement that they are not good surgeons. They have other things at which they are good, even excellent. In my opinion there are several reasons for the observation. Sentinel node biopsy requires the surgeon to possess certain characteristics and qualities. It requires a well-developed ability to think in a three-dimensional fashion because the surgeon needs to translate the one-dimensional probe readings and the two-dimensional scans into a three dimensional image in his or her head. Not everybody can do this well. Another factor is that lymphatic mapping requires the skill to operate in a confined space, through a small incision, deep in the axilla. The surgeon must have the ability to dissect delicate lymphatic in a tight location. Some surgeons are good at the big operations; for lymphatic mapping one needs to be good at the small operations. And last but not least, the surgeon must not be in a hurry. Charlie Cox, the famous breast surgeon from Tampa, says the surgeon ought to sit down to do sentinel node biopsy. He has got a point. Sometimes, the sentinel node is found within one minute, but other times it takes more than an hour to find one tiny node from which one can squeeze just a few ‘counts’. So, lymphatic mapping requires a lot of patience. Now, if the average Indonesian surgeon is anywhere like the average Dutch surgeon, then, when one considers the many extraordinary qualities that they possess, patience is not necessarily the first one to spring to mind. Indeed not if one contemplates the average surgeon, and when it comes to taking your time and being patient, I am afraid that surgeons everywhere are very average.

Table 1. Purposes of lymphoscintigraphy.

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<td>To point out the draining lymph node field at risk for metastatic disease</td>
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<td>To indicate the number of sentinel nodes</td>
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<td>To help distinguish first-tier nodes from secondary nodes</td>
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<td>To identify sentinel nodes on unpredictable locations</td>
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<td>To mark the location of sentinel node on the skin</td>
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REFERENCES


