Sentinel node biopsy. Evolving from melanoma to breast cancer

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CHAPTER 1

INTRODUCTION
CHAPTER 1

SENTINEL NODE BIOPSY
EVOLVING FROM MELANOMA TO BREAST CANCER

The sentinel node is the first lymph node that receives lymphatic drainage from a malignant tumour and is therefore the first node to contain metastasis if lymphatic dissemination occurs\(^1\) (Fig. 1). In 1977, Cabañas first described a technique for identification of the sentinel node in patients with penile cancer\(^2\). He determined which node was the sentinel node guided by anatomical landmarks (Fig. 2). The reproducibility of this technique was shown to be limited\(^3\). In 1992, Morton also described a technique for identification of the sentinel node for staging patients with melanoma. He used a blue dye to visualise the lymphatic duct and followed it to the sentinel node\(^1\) (Fig. 3). In 1993, Morton, Nieweg, Meijer and Krag added a gamma probe for intraoperative identification of the sentinel node in patients with melanoma\(^4^7\) (Fig. 4). That same year, the first study was published describing the application in patients with breast cancer\(^8\).

Fig. 1 The sentinel node is the first lymph node that receives lymphatic drainage from a malignant tumour and is therefore the first node to contain metastasis if lymphatic dissemination occurs. Neth J Med 1996; 140: 2235-9. Reprinted by permission of the editors.
Fig. 2 Cabañas first described the sentinel node concept in 1977. He localised the sentinel node by measuring the distance from the pubic tubercle and the inguinal ligament. CANCER, Vol. 39, No. 2, 1977, page 456-66. Copyright © 1977 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Fig. 3 Morton et al. introduced the use of blue dye for lymphatic mapping. A few minutes after injection of the blue dye at the tumour site, the first draining lymph node stains blue and can easily be recognised among non-sentinel nodes.
Sentinel node biopsy as proposed by Morton et al. has gained enormous popularity in a few years time. An increasing number of investigators assess the feasibility and reliability of the procedure and seek for optimisation of the technique. More than 200 reports on sentinel node biopsy were published in the first nine months of 1999. Several courses have been organised at The Netherlands Cancer Institute and elsewhere to fulfil the need for training of surgeons and nuclear medicine physicians. In April 1999, the First International Congress on the Sentinel Node in Diagnosis and Treatment of Cancer was organised in Amsterdam, the Netherlands. An overview of trials on sentinel node biopsy in patients with melanoma is given in Table 1. A similar table for breast cancer is presented in chapter 7.
**Table 1. Results of sentinel node biopsy by various investigators in studies with at least 100 patients. The percentage of false negative cases is calculated over the total number of node-positive patients.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N. of patients</th>
<th>Technique</th>
<th>SN = sentinel node, S = sentinel lymph node, N.A. = not available</th>
<th>VA = not available in all patients</th>
<th>ELND in all patients</th>
<th>ELND = elective lymph node dissection, N.A. = not available</th>
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<td>Motion</td>
<td>1991</td>
<td>766</td>
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<td>766</td>
<td>223</td>
<td>1991</td>
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<th>Author</th>
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<tr>
<th>Range (months)</th>
<th>Median or mean follow-up in months</th>
<th>No. of false</th>
<th>No. of patients with Incomplete</th>
<th>N. of false cases (%)</th>
<th>Positive SN (%)</th>
<th>Identified sites SN</th>
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<th>(years)</th>
<th>5 (6)</th>
<th>2 (70)</th>
<th>78</th>
<th>B</th>
<th>223</th>
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<td>72 (2)</td>
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<td>56</td>
<td>B + S +</td>
<td>816</td>
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<td>15 (3)</td>
<td>1 (71)</td>
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<td>26 (4)</td>
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<td>32 (5)</td>
<td>6 (78)</td>
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Since 1998, the number of publications concerning breast cancer exceeds that of papers on melanoma (Fig. 5). This evolution is not surprising for two reasons, the first being that the incidence of breast cancer is five times that of melanoma. The incidence in the Netherlands was about 9500 versus 1850 cases in 1995\(^9,10\). Breast cancer is the most common form of cancer in women in many countries. The second reason is that sentinel node biopsy has a different impact on treatment in either group: in patients with melanoma, the technique is performed as an extra procedure with no well established benefits, whereas it can prevent routine lymph node dissection in patients with breast cancer.

![Fig. 5 Number of publications on sentinel node biopsy for melanoma and breast cancer until September 1999.](image)

**THE ROLE OF SENTINEL NODE BIOPSY FOR PATIENTS WITH MELANOMA**

Lymph node status is an important prognostic factor for patients with melanoma\(^1,11,14\). Ten-year survival is worse when lymph node metastases are palpable (20-30\%) than when the lymph nodes are clinically uninvolved (45-55\%)\(^1,11,13,15\). About 20\% of patients with clinically uninvolved nodes have regional metastases. Early removal of tumour-positive lymph nodes has the potential to cure patients\(^11,12,16\). Elective
lymph node dissection for clinically localised melanoma is, however, controversial because a survival benefit has not clearly been shown. Complications of lymph node dissection are frequently seen, especially after groin dissection. Therefore, the WHO no longer recommends to perform elective lymph node dissection. Wide local excision of the tumour alone is currently the treatment of choice in the Netherlands for clinically localised melanoma.

Now that the technique of sentinel node biopsy has become available for staging, the debate has shifted from elective lymph node dissection to selective lymph node dissection, i.e. the removal of regional lymph node basins only if there is microscopic involvement of the sentinel node. It is yet unknown whether this approach is beneficial to patients with melanoma. The final validation has to come from a randomised prospective study. The Multicenter Selective Lymphadenectomy Trial, initiated by Morton, has been designed to establish the impact of sentinel node biopsy on survival, morbidity, quality of life, recurrence pattern and costs. Patients with a melanoma of at least 1 mm thickness according to Breslow or level IV according to Clark are randomised to undergo either wide local excision and sentinel node biopsy or wide local excision alone. Regional node dissection is performed in case of involvement of the sentinel node or later if lymph node metastases become palpable. Up till September 1999, 1300 patients have been accrued. The Netherlands Cancer Institute participates in this trial since August 1995 and has entered 140 patients. This study may reveal the potential benefit of sentinel node biopsy in a few years time.

An advantage of staging clinically uninvolved lymph nodes would be that it identifies patients with high-risk for recurrence who may be candidates for adjuvant therapy. Sentinel node status is an important prognostic factor. It has been suggested that patients with a relatively low tumour burden may benefit most from adjuvant treatment strategies, which is typically the case in sentinel node-positive patients. The possibilities for adjuvant therapy are however limited. Kirkwood et al. reported an improvement of median survival from 2.8 to 3.8 years with interferon-alfa2b in high-risk patients. This regimen was poorly
 tolerated. New studies have been started to confirm the survival benefit found by Kirkwood et al. or to find tolerable doses of interferon,$^{28,31}$ other studies focus on melanoma vaccines.$^{32}$ Because adjuvant treatment for melanoma is still at an experimental stage and is therefore not routinely offered to patients in the Netherlands, diagnosis of clinically occult lymph node metastases has no significant impact on treatment choice.

**THE ROLE OF SENTINEL NODE BIOPSY FOR PATIENTS WITH BREAST CANCER**

In contrast with melanoma, elective lymph node dissection has been part of the routine treatment of breast cancer since it was proposed by Halsted (1852-1922). The axillary lymph node status is an important parameter that indicates the need for adjuvant systemic treatment. Effective adjuvant treatment is available and widely accepted.$^{33,34}$ It leads to around 25% reduction of mortality. Lymph node dissection also assures regional tumour control and improves survival.$^{35,36}$ Axillary clearance is associated with significant morbidity. Numbness, pain, weakness, stiffness and swelling of the arm are common complaints. Although these complaints are usually not severe, the incidence is high.$^{37}$ Chronic lymphedema is the most feared complaint. It is seen in about 8% of patients after axillary surgery alone and in 20-30% of patients if the axilla is also irradiated.$^{38}$ About 60% of patients who are subjected to axillary clearance do not have lymph node metastases. These patients do not benefit from surgery and are unnecessarily at risk for complications.

Sentinel node biopsy has the potential to replace axillary clearance for staging breast cancer.$^{39}$ It has been shown to be an accurate method for staging.$^{8,40,43}$ Axillary clearance can be avoided if the sentinel node is free of disease. Patients undergoing sentinel node biopsy do not need a suction drain for the axilla, they will experience less postoperative morbidity and can be discharged soon after surgery which will reduce costs. Caution is warranted because some groups reported that up to 20% of node-positive patients were missed (Chapter 7).
The sentinel node is the first lymph node that receives lymphatic drainage directly from a malignant tumour. When a tracer is injected at the site of the tumour, the particles are taken up into the lymphatic channels and accumulate in one or more lymph nodes in the regional lymph node basin. This lymphatic flow can be visualised with dynamic lymphoscintigraphy after injection of a radioactive tracer such as $^{99m}$Tc-nanocolloid. During surgery, vital blue dye can be used to visualise the afferent lymphatic vessels in the lymph node basin and to stain the draining sentinel nodes.

How do we know during surgery which node is a sentinel node? Several definitions are in use. Morton et al. used only the blue dye and defined a sentinel node as any node with a blue afferent vessel. Krag et al. did not use the blue dye and labelled a node as sentinel node if the probe registered at least 25 counts per 10 seconds. If there was more than one hot node, the hottest one was regarded as sentinel node. When both tracers are used, the definition can become confusing because some hot nodes may not be blue. Uren et al. used both lymphoscintigraphy and blue dye and defined a sentinel node as any draining node that was seen to receive direct lymphatic drainage from the biopsy site.

At the Netherlands Cancer Institute, a similar definition is used as by Uren et al. A lymph node is considered to be a sentinel node when a blue afferent lymphatic vessel is identified coming from the injection site and leading to this node. If no blue dye is seen during exploration, which occurs in about 9% of the lymphatic basins in patients with melanoma, the nodes are sought that were identified as sentinel nodes on scintigraphy. A hot spot on lymphoscintigraphy is regarded to represent a sentinel node if an afferent lymphatic vessel coming from the injection site is visualised. If no afferent vessel is identified, the first hot spot in each basin that appears on the lymphoscintigraphy images is considered to represent the sentinel node. Hot spots appearing subsequently are regarded as non-sentinel nodes.
PART I: MELANOMA

Chapter 2 of this thesis describes the technique of lymphatic mapping and sentinel node biopsy for staging patients with melanoma. At The Netherlands Cancer Institute, a combined technique is used with lymphoscintigraphy, a gamma probe and patent blue dye\(^49\). Most groups take this approach\(^49\)\(^-\)\(^53\), since the techniques are complementary. Lymphoscintigraphy provides the road map for the surgeon, the gamma probe guides the dissection towards a sentinel node before the surgeon can see it, and the patent blue dye provides detailed insight in the anatomic configuration of lymphatic structures. The sentinel node can thus be identified in 95-100% of patients\(^7\)\(^-\)\(^58\).

In general, no lymph node dissection is performed if the sentinel node is tumour-negative. Whether the identification was truly reliable can only be proven during follow-up. Over 200 patients with melanoma underwent sentinel node biopsy at The Netherlands Cancer Institute since October 1993. Chapter 3 evaluates the outcome after sentinel node biopsy at a median follow-up of 32 months.

Preoperative lymphoscintigraphy is an important part of lymphatic mapping\(^59\). The images may however suggest a different lymphatic drainage pattern than the intraoperative lymphatic mapping with blue dye. Chapter 4 describes the typical differences between the two modalities. Both surgeons and nuclear medicine physicians should be aware of these pitfalls to prevent false-negative biopsies.

Lymphatic mapping in the head and neck area is more complicated than in groin or axilla because there is a large number of small nodes in a fine meshwork of lymphatic vessels in close relation to vital structures. Sentinel node biopsy for melanoma in this region is therefore evaluated separately in chapter 5. This study was the result from co-operation between The Netherlands Cancer Institute and the Groningen University Hospital.

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PART II: BREAST CANCER

The second part of this thesis concerns the application of sentinel node biopsy in patients with breast cancer. The first procedure in a patient with breast cancer at The Netherlands Cancer Institute was performed in January 1997. In January 1999, the decision was made to perform no axillary node dissection if the sentinel node is tumour-negative. Over 200 patients with breast cancer now have undergone the procedure. The technique as used in patients with melanoma has been adjusted somewhat. This is the subject of chapter 6.

Chapter 7 gives the results of our initial study in which the technique was validated by performing axillary node dissection regardless of sentinel node status. This study was performed in co-operation with the Groningen University Hospital.

The sentinel node can be identified by the surgeon almost as often as in patients with melanoma, but the preoperative imaging is more often unsuccessful. In chapter 8 and 9, an attempt is made to quantify and explain the less efficient uptake of radioactive colloid in lymph nodes after injection in the breast.

Sentinel nodes are found outside the axilla in as much as a fifth of our patients. The majority of such nodes is located in the internal mammary chain. Treatment of the internal mammary chain nodes is controversial, but lymphatic mapping may be a method to identify a small subgroup of patients who can benefit. Chapter 10 addresses this issue and in chapter 11 two cases are described where metastases were found in the internal mammary chain whereas the axilla was tumour-free.

Chapter 12 discusses the future perspectives of lymphatic mapping and sentinel lymphadenectomy.
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**INTRODUCTION**


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