In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma

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CHAPTER 1

Introduction and outline of the thesis
Introduction

Metastatic spread in breast cancer and melanoma can occur through two separate pathways, via the lymphatic vessels and via the blood stream. Lymphatic dissemination often happens first. The Greek doctor Hippocrates (460-377 B.C.) was the first one known to describe cancer. He compared the disease with a crab, *Kαρσινοζ* in Greek, an animal that holds on tight once it has grabbed something with its pincers. Hippocrates was aware of the existence of the lymphatic system and even described the clinical picture of lymph node metastases. Thomas Bartholin (1616-1680) was one of the first people to identify lymph vessels in a human being and called them *vasa lymphatica*, *lympha* being Latin for clear spring water. Bartholin was of the opinion that lymph was fluid filtrated from blood. In the nineteenth century, Virchow (1821-1902) proposed the theory that lymph nodes filter particulate matter from lymph. He suggested that specific parts of the human body drain to a common lymph node and subsequently to several other lymph nodes. Virchow suggested that metastases spread in the same orderly fashion. This concept of stepwise dissemination led to the awareness that cancer could be cured at an early stage with adequate surgery. Sentinel node biopsy is based on this concept of an orderly pattern of lymphatic drainage from a primary tumour to a regional lymph node basin. The lymph node on a direct drainage pathway from the tumour is supposed to be the first to filter out and harbour tumour cells. This lymph node is referred to as the ‘sentinel node’. Virchow’s concept that lymph from various parts of the body drains via specific pathways to specific lymph nodes gradually caught on.

The first person known to have used the term ‘sentinel’ with reference to lymph nodes was Braithwaite in 1923 who mentioned ‘glands sentinel’ when he reported studies using blue dye to investigate lymphatic drainage. In 1951, Gould performed frozen section analysis on a lymph node found at the junction of the anterior and posterior facial vein during a total parotidectomy. The intraoperative pathologic examination of this lymph node revealed metastasis and subsequently a radical neck dissection was performed. From then on, he carried out a neck dissection for parotid cancer only if the node at this specific location contained metastasis. In 1966, Chiappa and co-workers identified primary testicular lymph centres when performing lymphangiographic studies in patients with testicular carcinoma. In 1970, Kett et al. injected blue dye in the areola of the breast and administered contrast medium in the visualised lymphatics to observe the drainage. The dye was seen travelling to an isolated lymph node, the ‘Sorgius’ node, through which lymph subsequently flowed towards lymph vessels around the axillary vein. Haagensen stated in 1972 that a specific group of lymph nodes in the lower axilla were most often the only nodes involved in breast cancer patients. In 1977, Cabañas performed lymphangiographic studies that repeatedly showed direct drainage from the penis to a specific lymph node near the superficial epigastric vein that appeared to be the primary site of metastases. Christensen
observed ‘primary draining nodes’ using breast lymphoscintigraphy in 1980. The first report on the intraoperative use of a gamma-ray detection probe concerned a patient with rectal cancer and was published in 1984. Aitken et al. injected antibodies of a foetal antigen labelled with iodine-131 and measured a higher count in a rectal tumour than in the surrounding tissue. Later on, the probe was used to find metastases in colon cancer and to detect bone metastases. Morton, Cochran and co-workers at the John Wayne Cancer Institute in Santa Monica, introduced lymphatic mapping with the help of blue dye. They injected blue dye intradermally at the primary tumour site in melanoma patients. An incision was subsequently made over the lymph basin where the sentinel node was expected and they meticulously dissected the blue lymphatic channel leading to the first draining lymph node. Sentinel node biopsy in breast cancer was also first performed at the John Wayne Cancer Institute, as reported by Giuliano and colleagues in 1991. The injection of a radiopharmaceutical with preoperative lymphoscintigraphy and intraoperative use of a gamma-ray detection probe was added for more accurate localization of sentinel nodes. This combination is successful in the vast majority of patients.

Several lymphatic mapping techniques are nowadays applied all over the world. At the Netherlands Cancer Institute, the combined use of the above-mentioned tools enables identification of a sentinel node in almost every patient. The concept of sequential dissemination through the lymphatic system was confirmed in a laboratory study and lymphatic mapping was embedded in our routine management.

Although the multidisciplinary approach of surgeons, nuclear medicine physicians, radiologists and researchers has generated many new insights, numerous questions concerning this approach have not yet been answered. In this thesis, the validation of the sentinel node procedure in breast cancer and potential new indications are described. In melanoma, the relevance of the size and the location of a sentinel node metastasis, and possible implications for further lymph node dissection are discussed. Also, a new imaging technology for lymphatic mapping, single photon emission computed tomography camera with integrated CT (SPECT/CT), is introduced and evaluated for both breast cancer and melanoma.

Chapter two provides a general description of the status of lymphatic mapping for breast cancer and melanoma at the time we began these doctoral thesis studies.

Breast cancer

Chapters three through eight focus on the sentinel node procedure in breast cancer patients with the aim to validate the procedure, to refine the technique and to expand its indications. Sentinel node biopsy became standard of care before consensus on the technique was reached and without randomized studies having shown the relative risk
of axillary recurrence and the impact on survival rate after long-term follow-up. In **chapter three**, a systematic literature review is presented concerning patients with a tumour-negative sentinel node and no subsequent axillary node dissection. The axillary recurrence rate was determined and an attempt was made to compare the outcome for the various techniques of lymphatic mapping.

In order to make sure that we remove the very lymph node that receives the lymph fluid from the breast cancer, we administer the tracer fluids in the actual breast cancer, which is different from what is done in most other places. **Chapter four** describes the lymph node recurrence rate in the axilla and elsewhere and the survival in sentinel node-negative patients using this approach. The false-negative rate was also determined.

In a minority of breast cancer patients, lymphoscintigraphy demonstrates only a sentinel node outside the axilla. In **chapter five**, the yield of axillary exploration using of blue dye and a gamma-ray detection probe is described in such patients. Instead of performing axillary node dissection if no node is found in this region, patients are spared further dissection at our institute, based on the hypothesis that a sentinel node is not necessarily located in the axilla. The results of this axilla-sparing approach were evaluated.

Treatment of disease in the breast or the axilla in the past may have damaged lymphatics, which may have changed the drainage pathways. **Chapter six** reports a study on the lymphatic drainage patterns based on preoperative imaging and the operative findings in breast cancer patients who had undergone previous treatment of the breast or the axilla. The patients were divided in subgroups according to the previously performed treatment. The lymphatic drainage patterns in the subgroups were compared to the whole study population and to the pattern that had been found in an earlier study of patients without prior breast treatment.

**Chapter seven** describes a similar analysis for breast cancer patients who had been diagnosed with Hodgkin’s lymphoma for which they received mantle field radiation to the neck, the axilla and the mediastinum, overlapping part of the breast.

**Melanoma**

Chapters eight through eleven describe attempts to better adjust the treatment of melanoma patients with an involved sentinel node to the needs of the individual situation. Several investigators have attempted to identify patients who may benefit from a completion node dissection if the sentinel node biopsy reveals metastasis and to distinguish these patients from the ones who do not need further treatment. The extent of the disease in the sentinel node is one of the parameters to base such a selection on. **In chapter eight**, three micromorphometric parameters of sentinel node metastases were compared: invasion depth from the capsule (Starz-classification), maximum
diameter (Rotterdam-criteria) and location within the node (Dewar-classification). The purposes of this study were to determine which classification best predicts additional lymph node disease and survival, and to suggest a threshold below which a completion dissection may be omitted.

Starz et al. suggested that melanoma patients with a sentinel node metastasis invading no more than 1.0 mm below the capsular level can be spared further surgery. This policy was prospectively evaluated and the results are described in chapter nine.

The extent of a groin dissection in case of an involved sentinel node is controversial. In fact, the issue whether or not lymph node dissection should be performed at all is subject of discussion. Early conventional lymphoscintigrams can distinguish a sentinel node from subsequent nodes and the new SPECT/CT technology that will be discussed in the last chapters of this thesis shows their precise anatomical location. This knowledge can guide the extent of a groin dissection in sentinel node-positive patients. Chapter ten describes the results of a strategy to perform a superficial lymph node dissection when sentinel nodes and second-tier nodes are confined to the femoro-inguinal area, and to add a deep dissection in the remainder of the patients. This approach was based on the concept that a second-echelon node is the next one at risk for additional metastasis in case of a tumour-positive sentinel node.

In chapter eleven, lymphatic drainage patterns to the groin were analyzed by conventional lymphoscintigraphy and SPECT/CT. The implications for the extent of a groin dissection were determined based on the location of the sentinel node and second-echelon nodes in the different zones of the groin.

SPECT/CT

Conventional lymphoscintigraphy shows the radiopharmaceutical that is accumulated by the sentinel node, but it does not depict the anatomic structures that enable its precise location. Lymphatic drainage patterns are variable. They may be unusual, difficult to interpret, or may not be shown at all. Hybrid SPECT/CT was recently introduced to overcome such difficulties. SPECT is a tomographic version of conventional lymphoscintigraphy and the images have a high contrast and resolution. When fused into one image with the anatomical details provided by CT, a meaningful surgical ‘roadmap’ is created. Chapters twelve through eighteen cover the results obtained with this new technology.

Chapter twelve describes our first experience with SPECT/CT for lymphatic mapping in patients with breast cancer or melanoma.

Chapter thirteen presents a literature review of the differences in the technique that is used by various investigators and of the results of lymphatic mapping using both
conventional imaging and SPECT/CT in breast cancer patients.

In **chapter fourteen**, SPECT/CT is explored in the minority of breast cancer patients in whom no sentinel node is depicted on the conventional lymphoscintigrams. The roles of blue dye and careful intraoperative palpation of the axilla were evaluated in patients in whom no axillary sentinel nodes were detected by either conventional imaging or SPECT/CT.

The relevance of the advantages of SPECT/CT for the surgical procedure are the subject of **chapter fifteen** for breast cancer patients and **chapter sixteen** for melanoma patients.

In **chapter seventeen**, a new SPECT/CT imaging technique is presented that was introduced only recently. The new volume-rendered SPECT/CT shows the surrounding skin, muscles and bones, providing a three-dimensional insight in the location of sentinel nodes. The value of this approach is described for lymphatic mapping in patients with breast cancer or melanoma.

The reliability of lymphatic mapping depends on the accurate visualization and identification of the sentinel node(s). It has been suggested, that extensive metastatic involvement can prevent lymph fluid from entering the (original) node, which may lead to rerouting of lymph fluid to another lymph node. If such a ‘neo’-sentinel node does not yet contain tumour, this results in a false-negative procedure. So far, there has been little evidence to support this hypothesis. SPECT/CT enabled a study of this concept of lymph flow blockage in patients with proven metastatic nodes, as is presented in **chapter eighteen**.

The thesis ends with a general summary of the different chapters, conclusions and future prospects of the sentinel lymph node biopsy. A general summary is also given in Dutch and Spanish.
References