Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
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CHAPTER 1

INTRODUCTION
In this new era of more and more conservative surgical treatments, the sentinel node procedure is gaining ground. This delicate staging procedure is now being implemented in more than a dozen types of cancers. Where did it all start?

The first reference found in the literature regarding the use of the English term ‘glands sentinel’, was in 1923 by Braithwaite, who reported studies of lymphatic drainage using vital dye injections. However, the German pathologist Virchow already described the concept of lymphatic drainage to a specific lymph node in the mid-nineteenth century. In an article by Gould et al. in 1960, the term ‘sentinel node’ was used when he described that during a total parotidectomy in 1951, a normal-appearing node was noted at the junction of the anterior and posterior facial vein and was sent in for frozen-section diagnosis. The pathology report said “lymph node with metastatic tumor” and the decision was then made to perform radical neck dissection. Hereafter, similar procedures were carried out while referring to this specific lymph node as a ‘sentinel node’.

Then in 1977, the Paraguayan surgeon Ramon Cabañas described a ‘sentinel lymph node’ in penile cancer. He suggested that squamous cell carcinoma of the penis initially drains to a particular lymph node in the groin, which was constantly found to be in a same anatomical position. This is not peculiar, because penile cancer itself is also always located in the same location, unlike melanoma or even breast cancer.

However, it was Donald Morton, surgeon at the John Wayne Cancer Center in Santa Monica, with his pathologist Alistair Cochran from the University of California Los Angeles who took sentinel node biopsy a major step forward. They proposed the groundbreaking concept of ‘lymphatic mapping with sentinel lymph node biopsy’ for melanoma in the late 1980’s. They suggested that a melanoma could drain to any node in a particular lymph node field, depending on the location of the primary lesion and with a certain individual variability. Therefore, any node in such a lymphatic field can be a sentinel node.

It has now been proven that lymphatic mapping enables more accurate staging because the pathologist receives the lymph node(s) at the greatest risk of harboring metastatic disease. The pathologist is inclined to obtain multiple sections and use sensitive immunohistochemistry staining techniques in addition to the standard hematoxylin and eosin staining. Lymphatic mapping also allows patients with lymph node metastasis to be treated in an early phase without submitting other patients to unnecessary regional lymph node dissection. Additionally, more patients are identified who may benefit from adjuvant systemic therapy.

In three preceding theses from this institute, the validation, methodology and implications have been discussed. This thesis deals with the more clinical aspects of the sentinel node procedure. Fine-tuning of the sentinel node technique in breast cancer patients, its clinical relevance and follow-up events such as morbidity and false negative results are evaluated. Regarding melanoma, the technique has now matured to the point that consensus has been reached on how the procedure should be performed. Only its clinical relevance and follow-up events such as morbidity and survival are discussed.

Outline of the thesis
The first eight chapters following this introduction deal with the sentinel node procedure in breast cancer. Chapter 2 gives an overall introduction. Topics such as inclusion criteria, drainage patterns, false-negative procedures and clinical relevance of extra-axillary sentinel nodes are reviewed.
The next three chapters deal with the refinement of the sentinel node technique. In contrast to the situation in melanoma, there is a large variability in tracer administration techniques in patients with palpable or non-palpable breast cancer. In general terms, injection techniques may be classified as superficial or deep. The advantages and disadvantages of the intratumoral injection technique are discussed in Chapter 3.

Chapter 4 describes the difference in lymphatic drainage from the breast if two different injection techniques are used. A situation is reported in which a patient with a non-palpable lesion received an intraparenchymal tracer injection by accident and an intratumoral injection the next day.

If an intratumoral injection technique is used, one can wonder if the sentinel node technique can still be performed after the primary tumor has been removed. Possible failure of the technique might be due to the disruption of breast lymphatics. Chapter 5 describes a prospective study that examines the reproducibility of lymphoscintigraphy in patients before and after excisional biopsy of a breast lesion.

Interest in drainage patterns of breast cancer is growing since the introduction of the sentinel node procedure. How often is drainage to extra-axillary sentinel nodes observed? Is there any disparity in drainage patterns from different quadrants of the breast? These two questions are answered in Chapter 6. Our intratumoral tracer injection technique enables accurate visualization of drainage from the actual primary tumors. Whether or not internal mammary chain sentinel nodes should be pursued is discussed in Chapter 7. Incidence, identification, tumor status, stage migration and changes in management are given.

The success of the sentinel node procedure is, in addition to the identification, determined by a low false negative rate. At recent meetings of the American and European Societies of Surgical Oncology, confusion was sensed over the definition of a false negative result. In Chapter 8, three credible definitions of a false negative finding in sentinel node procedures are given and discussed. Our experience with false negative sentinel node biopsies and what we have learned from these cases is shared in Chapter 9.

The next two chapters are devoted to the sentinel node procedure in melanoma patients. A long median follow-up of six years and a large group of 250 patients enable a good evaluation of the complications, morbidity, recurrences and survival. This is discussed in Chapter 10, together with the visualization and identification rates of the sentinel nodes. Although there is a tendency to make the sentinel node procedure part of standard management in patients with clinically localized melanoma, some unfavorable information has been reported that makes one question its routine use. The incidence of in-transit metastases in patients with a tumor-positive sentinel node has been suggested to be fairly high but numbers vary greatly between different institutes. In Chapter 11, the incidences of in-transit metastases after lymph node dissections for a tumor-positive sentinel node and because of palpable nodal metastases are compared.

This thesis ends with a general conclusion and a description of future prospects (Chapter 12).
REFERENCES