Methodology and implications of lymphatic mapping and sentinel lymphadenectomy
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CHAPTER ONE

Introduction and Outline of the Thesis
T
he sentinel node concept as theory underlying selective lymphadenectomy has gone through a long developing process. The concept is based on the hypothesis that lymphatic drainage follows an orderly and predictable pattern to a regional lymph node basin. Consequently, the initial lymph node that drains the primary tumour will be the first to be involved when tumour dissemination occurs. The description of this lymph node as a “sentinel node” first appeared in the literature in 1960. Despite some reports thereafter, the impact of establishing the sentinel node status was not fully appreciated. At the time Morton and Cochran presented a poster about the technique of lymphatic mapping at the WHO’s Second International Conference on Melanoma in 1989, nobody realised that this was the beginning of a new era in surgical oncology. Eventually, the sentinel node concept has evolved from an underestimated principle to a generally accepted and world-wide applied theory.

Lymphatic mapping with sentinel node biopsy serves various purposes, related to its application in several malignancies. In melanoma, sentinel node biopsy can identify occult lymph node metastasis at expected and unexpected locations, providing prognostic information and a selection criterion for entering patients in adjuvant systemic therapy trials. Improving survival is another aim by enabling early lymphadenectomy. This will be one of the endpoints of the Multicenter Selective Lymphadenectomy Trial initiated by Morton in which patients are randomised between “wait and see” policy and sentinel node biopsy. Total accrual in September 2001 was 1897 patients. In breast cancer, the primary aim was to reduce morbidity associated with routine axillary lymph node dissection. With refinement of the pathological examination, detection of (micro)metastases in the sentinel node has been improved resulting in better staging. Identification of extra-axillary sentinel nodes improves staging as well. Reduction of morbidity associated with complete regional lymph node dissections and improvement of staging are also the primary aims of selective lymphadenectomy in other malignancies like gynecological cancers, urological cancers, gastro-intestinal cancers, thyroid cancer, lung cancer and head and neck squamous cell carcinoma. In general, lymphatic mapping enables visualisation of aberrant drainage pathways and facilitates scrutinising the lymph node with the highest risk of harbouring metastasis by the pathologist. After validation of the sentinel node concept as described in two preceding theses from our institute, methodology and implications of the technique have become important issues. This thesis deals with these aspects, mostly related to breast cancer.

The first three chapters following this introduction (chapter one) provide the reader background information about several topics related to selective lymphadenectomy. In chapter two, the interesting evolution of lymphatic mapping is described and placed in a historical context. Chapter three deals with an important conceptual issue. The definition of a sentinel node is still liable to discussion and confusion. Morton’s definition a sentinel node is the initial lymph node upon which the primary tumour drains is a clear and correct one, but sometimes difficult to handle in clinical practice. Alternative definitions based on anatomy or technical elements of the sentinel node biopsy are attractive, but have their drawbacks. One of these practical
definitions, a sentinel node is the hottest node, has been shown to be inaccurate by several studies in both melanoma and breast cancer. This definition and other definitions of a sentinel node are discussed from theoretical and practical points of view in chapter three. **Chapter four** entails a review concerning the anatomy and physiology of lymphatic drainage of the mammary gland. Knowledge of this subject that has been gained during the last three centuries is described and discussed in the context of the application of sentinel node biopsy in breast cancer. The next six chapters contain analyses of several methodological aspects concerning lymphatic mapping and sentinel lymphadenectomy in breast cancer. The reproducibility of preoperative lymphoscintigraphy is described in **chapter five**. Variability of lymphatic flow is one of the potential causes of false-negative results. Therefore, this first report of assessing the reproducibility of lymphoscintigraphy in breast cancer is an essential step in the understanding of technical failure. **Chapters six and seven** describe our attempts to optimise the preoperative identification of the sentinel with the use of a radiolabelled colloid. Visualisation and radioactivity uptake of the sentinel node were influenced by adjustment of the tracer dose, colloid particle concentration, delayed imaging and repeat injection of the radioisotope. Etiological factors associated with non-visualisation of the sentinel node are given in chapter seven. **Chapter eight** addresses the technical adaptations that allow sentinel node biopsy in non-palpable breast cancer. These patients are ideal candidates for sentinel lymphadenectomy because of the low incidence of lymph node metastases. In addition, excision of the primary breast carcinoma is facilitated by the use of gamma ray detection probe as a result of intralesional administration of the radiolabelled colloid. In **chapter nine**, the reliability of intraoperative frozen section investigation of the sentinel node is described. The ability to perform an immediate completion lymphadenectomy with the use of this technique was evaluated in both melanoma and breast cancer. Besides the limited sensitivity which is more pronounced in melanoma, logistic difficulties may arise when the pathology laboratory is at a certain distance from the hospital. According to Gemignani and colleagues, the use of intraoperative frozen section analysis increases the charges of sentinel node biopsy and minimises its potential cost-saving advantages if compared with routine axillary lymph node dissection in breast cancer. These inherent disadvantages should be kept in mind when considering application of this technique.

**Chapter ten** describes the implications of finding non-axillary sentinel nodes in breast cancer. These sentinel nodes are mostly located in the internal mammary chain. Other non-axillary sentinel nodes are located in the breast parenchyma (intramammary), in the supra- or infraclavicular fossa, between the pectoral muscles (Rotter's node) or subcutaneously beneath the breast (paramammary or Gerota's node). The impact on staging and treatment of biopsy of these lymph nodes is discussed, relative to the findings in 555 sentinel node procedures. The following three chapters are related to lymphatic mapping in urological malignancies. **Chapter eleven** provides technical details about the application of lymphoscintigraphy in squamous cell carcinoma of the penis whereas **chapter twelve** focuses on the implications of this technique for staging and treatment of
clinically node-negative penile cancer. Preliminary results of lymphatic mapping in clinically stage I testicular cancer are provided in chapter thirteen.

Chapter fourteen describes an analysis of the learning phase for lymphatic mapping. Every new methodology requires experience of all involved disciplines, which implies that a certain number of procedures have to be performed in a controlled setting. This raises the question of how to determine that a sufficient quality has been achieved. The false-negative rate is the most important parameter in this discussion. The influence of group-size and critical value for non-identification or false-negativity on the decision about the quality of sentinel node biopsy is described from a statistical point of view.

Chapters fifteen and sixteen contain clinical cases of specific interest. The most frequent pitfall of lymphatic mapping is probably the blockage of ingress and uptake of tracers in a sentinel node by tumour. Tracers will be re-routed to a lymph node that is incorrectly labelled as sentinel node and this neo-sentinel node may still be tumour-negative in about 2% to 3% of the patients.\textsuperscript{25,26} One such case is described in detail in chapter fifteen. In chapter sixteen, two patients with an isolated internal mammary node metastasis are described and they illustrate the associated clinical problems, which have already been mentioned in chapter ten. This thesis winds up with a general discussion and description of recent developments in the field of selective lymphadenectomy (chapter seventeen).

References
