Sentinel node biopsy. Evolving from melanoma to breast cancer
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The aim of this thesis was to explore the feasibility of sentinel node biopsy in patients with melanoma or breast cancer and to improve the technique.

Chapter 1 introduces the concept of sentinel node biopsy. 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. The presence of lymph node metastases influences the choice for further treatment because it is associated with a worsened prognosis. The sentinel node or nodes can be identified by injecting a vital dye, a radioactive tracer or both at the tumour site. The tracers are taken up into the lymphatic system and drain to the sentinel node(s). The sentinel node(s) can thus be distinguished from other lymph nodes in the same basin. The major advantage of this technique is that lymph node status can be established reliably without removing all neighbouring lymph nodes. The technique was introduced for staging patients with melanoma in 1992. The successful introduction of this technique in patients with breast cancer increased the interest around the world rapidly in subsequent years.

Part I of the thesis describes the application of lymphatic mapping and sentinel node biopsy in patients with clinically localised melanoma, part II discusses the application of the technique in patients with early breast cancer.
Chapter 2 describes the technical details of sentinel node biopsy for staging patients with melanoma. A combined technique with preoperative lymphoscintigraphy and intraoperative identification with blue dye and a gamma ray detection probe is to be preferred. Lymphoscintigraphy reveals sentinel nodes in 95-100% of patients. It can be performed with a small particle colloid labelled with 99m-Technetium between one and 36 hours before surgery. The blue dye is injected at the start of the operation. It facilitates sentinel node identification by visualising the course of the lymphatic vessels. When a gamma probe is used additionally, sentinel nodes can be found in more than 95% of patients. Intraoperative frozen section examination is not recommended because sensitivity is low and metastases will be detected in only about 10% of all patients.

Chapter 3 provides insight in the reliability of sentinel node biopsy for staging patients with melanoma at The Netherlands Cancer Institute. The procedure was performed in 200 patients with a clinically localised melanoma of at least 1 mm thickness. A sentinel node was found and removed in 199 of 200 patients. Forty-eight patients (24%) had metastases in a sentinel node and underwent completion lymph node dissection. The patients were followed for a median of 32 months. Fifteen patients had recurrent disease after removal of a tumour-negative sentinel node. Six of them relapsed in the previously mapped basin (false-negative rate 6/54 = 11%). Sentinel node status and Breslow thickness were strong predictors of tumour recurrence and survival, even with a false-negative rate of 11%.

Chapter 4 focuses on lymphoscintigraphy. Although lymphoscintigraphy is indispensable for lymphatic mapping in patients with melanoma, the predicted number of sentinel nodes is accurate in
only 81% of the lymph node fields. In the remaining patients, intraoperative lymphatic mapping revealed that the true number of sentinel nodes was different from the number that was visualised with scintigraphy. The limited discriminating power of the gamma camera is the most important cause of discrepancies. Additional sentinel nodes were found by the surgeon because a lymphatic vessel was not seen on the lymphoscintigraphy in 43% of cases, a sentinel node was not visualised separately from other hot nodes or vessels or the injection site in 36%, or a sentinel node was blue and not hot (4%). Fewer sentinel nodes were found than suggested by scintigraphy because a lymphangioma was mistaken for a sentinel node (4%) or because a single elongated node, with afferent lymphatic ducts entering at opposite ends, was depicted as two hot spots (6%).

Chapter 5 describes the combined experience of The Netherlands Cancer Institute and the Groningen University Hospital with lymphatic mapping and sentinel node biopsy in 30 patients with melanoma in the head and neck area. Sentinel node biopsy in the head and neck region is a technically demanding procedure. In 27 of 30 patients, sentinel nodes were identified (90%). Only 53% of sentinel nodes were both blue and radioactive. The sentinel nodes were tumour-positive in eight patients and false-negative in two cases. Sensitivity of the procedure was 80% (8/10). Concentrating these procedures in a few high-volume centres may be necessary to establish sufficient accuracy.

PART II

BREAST CANCER

The technique of sentinel node biopsy in patients with breast cancer is described in detail in Chapter 6. The protocol used at The Netherlands Cancer Institute is adapted from that for patients with melanoma as
described in Chapter 2. The tracers are injected into the tumour in a smaller volume (0.2 ml). The lymphoscintigraphy images are completed after four hours instead of the two hours needed in patients with melanoma because the drainage of the tracer is slower after injection into the breast. Lateral scintigraphy images are performed in a prone position with a hanging breast to improve the view on the axilla. The identification rate is somewhat lower than in patients with melanoma: around 90%.

Chapter 7 describes a validation study performed at The Netherlands Cancer Institute and the Groningen University Hospital. Sentinel node biopsy was followed by axillary lymph node dissection regardless of sentinel node status in 136 patients with breast cancer. A sentinel node was visualised by lymphoscintigraphy in 118 patients (87%). During the operation a sentinel node was localised in 126 patients (93%). The sentinel nodes contained metastatic disease in 56 patients (44%). Three sentinel node biopsies were false negative (sensitivity 95%). In January 1999, the decision was made to perform lymph node dissection only if the sentinel node is tumour-positive or if it can not be found.

Chapter 8 focuses on the results of lymphoscintigraphy in patients with breast cancer. Sentinel nodes were initially visualised in only 83% of patients at The Netherlands Cancer Institute. Older age and lower dose were found to be associated with non-visualisation. After increasing the dose from an average of 60 MBq to 90 MBq, sentinel nodes were visualised in 94% of patients. A major advantage of injecting a small volume into the tumour is that the hot spot at the injection site is compact. Nodes close to the tumour are then not obscured and most of the radioactivity can be removed from the operative field with excision of the tumour. Besides that, lymphatic drainage to internal mammary chain nodes is frequently visualised with this technique (19%). The parasternal lymph nodes are a well known site for dissemination of breast cancer. Visualisation of these nodes with scintigraphy confirms that injection into the breast accurately reveals the lymphatic drainage pattern.
In Chapter 9, the amount of radioactivity present in sentinel nodes at the moment of surgery is quantified. Measurements were performed on all sentinel nodes of 51 patients with breast cancer and 22 patients with melanoma at 24 hours after injection of an average 64 MBq nanocolloid. Uptake in sentinel nodes of patients with breast cancer (median 6.0 kBq, 0.15% of the injected dose) is significantly lower than in patients with melanoma (median 33.3 kBq, 0.83% of the injected dose). The level of radioactivity decreases with time after surgery after correction for physical decay. No significant association was found between the level of radioactivity and age, sex, dose or nodal status. The small ranges of dose and age and the small number of patients may explain why dose and age were not found to be related to uptake. A two-day protocol is feasible but the operation should not be delayed unnecessarily.

Chapter 10 discusses the clinical relevance of biopsy of sentinel nodes that are located outside the axilla in patients with breast cancer. Lymphoscintigraphy reveals drainage to sentinel nodes in the internal mammary chain, in the interpectoral fossa, lateral or medial in the breast parenchyma or at level III of the axilla in 19% of patients with breast cancer. Biopsy of these nodes is technically demanding. It can be performed without additional morbidity. The clinical impact is limited: treatment changed in 3% of patients. It remains interesting to remove these nodes because this leads to more judicious use of adjuvant regional and systemic treatment.

Chapter 11 describes two patients with metastases of breast cancer in lymph nodes outside the axilla only. These cases illustrate the potential of lymphatic mapping and sentinel lymphadenectomy in patients with breast cancer.
CONCLUDING REMARKS

The procedure of lymphatic mapping and sentinel lymphadenectomy is valuable for staging patients with melanoma. However, it is necessary to prove whether the early detection and excision of clinically occult lymph node metastases leads to improved regional control and increased survival. Acute and long-term side effects have to be evaluated. The impact of adjuvant treatment at the early stage of lymphatic metastasis also has to be investigated prospectively. Sentinel node biopsy remains an experimental procedure in patients with melanoma until a survival benefit is proven or an effective adjuvant therapy regimen is available for patients with involved nodes.

Sentinel lymphadenectomy is of value in the staging and early regional treatment of patients with breast cancer. Several technical issues remain to be resolved. It is desirable to adopt a uniform method of performing the procedure around the world. Improvement of non-invasive imaging techniques for detection of regional lymph node metastases will probably decrease the number of patients that will have to undergo sentinel lymphadenectomy. Lymphatic mapping will decrease morbidity after surgery for breast cancer and will decrease the cost of primary treatment without jeopardising regional control and survival.