Melanoma surgery and the impact of sentinel node biopsy

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Chapter 1
Introduction and outline
INTRODUCTION

Melanoma

Benign naevi are common and harmless skin lesions caused by proliferation of melanocytes in the basal layer of the epidermis. These melanocytes produce melanin, which is then transported to the keratinocytes. Here, they protect the nucleus of the keratinocytes against UV radiation. Numerous stimuli are able to increase melanogenesis. Under influence of both environmental and genetic stimuli, uncontrolled proliferation of these melanin-producing cells can result in melanoma.

A melanoma is a malignant tumor originating from the abnormal growth of these pigment-producing melanocytes. This tumor occurs most often in the skin, but it can strike in any part of the body containing melanocytes, for example the mucosa of the upper earodigestive tract. [1] The incidence of melanoma is increasing continuously. By the year 2015 there will be 4800 new patients in the Netherlands compared to 4069 in 2008.[2] Approximately 15% of all cutaneous melanomas are located in the head and neck area and these will account for 720 new cases in 2015.

Sentinel node biopsy

Melanoma has the potential to metastasize through blood and lymph vessels. Early diagnosis before this occurs is important in order to achieve regional control of the disease. If a melanoma is suspected after physical examination and/or dermatoscopy, diagnostic excision is the subsequent diagnostic step. After pathologic verification, wide local excision of the tumour is advised with a margin of one centimetre for melanomas with a Breslow thickness of less than two millimetres and two centimetres for melanomas with a Breslow thickness above two millimetres. For cosmetic reasons limited excision margins are accepted in critical areas of the head and neck. In case of dissemination, lymph node metastases often precede haematogenous metastases. This notion prompted many surgeons in the past to perform elective lymph node dissection to stage the regional lymph node field and remove possible nodal metastases.[3-6] However, only 10-20% of patients, who underwent elective dissection of the regional node field, harboured tumour-positive lymph nodes.[7,8] In 1992, Morton and Cochran introduced the technique of sentinel node biopsy, which is based upon the stepwise dissemination of melanoma through the lymph nodes.[9,10] The sentinel node is defined as the lymph node upon which the primary tumor drains directly (Figure 1).[11] In 10-30% of all melanoma patients one or more tumour-positive sentinel nodes are found.[12-16] Early
studies showed that if the sentinel node is not involved, the rest of the regional lymph node basin is free of metastases as well.[12,15] Therefore, sentinel node biopsy is a diagnostic tool that helps to stage the regional node field.

Figure 1. The sentinel node is the node on a direct lymphatic drainage pathway.

Patients appreciate the prognostic information that the procedure provides.[13,17] Ten-year survival is 56% in patients with a tumor-positive node and 85% in case of a tumor-negative sentinel node.[18] Another advantage of the procedure is the possibility to identify patients with an involved sentinel node who may have more involved nodes and may benefit from completion lymph node dissection. Nevertheless, it is still unclear whether the chance to survive the disease improves in patients who undergo sentinel node biopsy compared to patients who are observed. The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) addresses this issue and a recent interim-analysis revealed a ten-year melanoma-related survival of 81.1% in patients who underwent sentinel lymph node biopsy and 77.3% if they were observed, but this difference did not reach statistical significance.[19] In the group of
patients with involved lymph nodes this comparison is more interesting. The ten-year survival of patients with an involved sentinel node and early completion lymph node dissection is 56.2% versus 40.8% for patients who received a completion lymph node dissection for palpable lymph node metastasis (p=0.01). The idea is that the sentinel node biopsy is a staging procedure that detects lymph node metastases and in combination with the therapeutic node dissection improves the chances to survive. Definitive results of the MSLT-I study are eagerly awaited.

On the other hand, sentinel node biopsy is also associated with several disadvantages. Increased operating time, higher costs, additional pre-operative imaging with exposure to ionising radiation, extra incisions and scars, and post-operative complications in 5-9% of these patients.[12,20,21] Also, several investigators suggested that the risk of developing in-transit metastases after early lymph node dissection in patients with a tumor-positive sentinel node could be increased.[22-24] Other studies could not confirm these findings and this issue is shrouded in controversy.[25,26] Furthermore, this diagnostic procedure is often false-negative with a range of eight to 32 per cent, even in renowned melanoma centers.[27-31] Regional node dissection is generally recommended for patients with a tumor-positive sentinel node, although additional lymph node metastases are found in only 10-20%.[32] It is unclear whether their chance of survival increases by the early lymph node dissection, while these individuals are exposed to the substantial morbidity of this procedure.[15,27,33-37] Hence, several investigators are trying to develop criteria to determine the risk that more nodes are involved in order to select patients who most likely benefit from completion node dissection.[38-41]

**Head and neck**

Sentinel node biopsy in the head and neck region is challenging because a third of the 600 lymph nodes in the body are situated in the neck.[42] The extensive network of lymph vessels and their sinuous routes also contribute to the complexity of lymph drainage in this region, with melanomas often draining to multiple and bilateral lymph nodes.[43-47] But also esthetics plays a role when performing sentinel node biopsy in this region.

Lymphatic mapping in the head and neck is challenging. Overprojection from the large amount of radioactivity at the nearby injection site may obscure a sentinel node on the images. Because of the large number of lymph nodes in the head and neck region, it is often hard to distinguish sentinel nodes from second-echelon nodes (Figure 2). The sensitivity of the sentinel node biopsy in head and neck melanoma is 80-100%.[42,48,49] The false-negative
rate was 20% in a recent review of 32 studies concerning 3442 head and neck melanoma patients.\cite{50} The results of sentinel lymph node biopsy are useful for staging and deciding on adjuvant treatment for patients with a head and neck melanoma.

\textbf{Figure 2.} Lymphoscintigraphy and SPECT-CT of a patient with a melanoma on the anterior face. This example shows that it is sometimes difficult to distinguish between first- and second echelon nodes.

The aforementioned issues do not only make the sentinel node biopsy technically difficult in the head and neck region, but they also resulted in a discussion about the extent of the completion neck dissection in patients with an involved cervical lymph node. Based on therapeutic neck dissections, in 1995 O’Brien et al describe the classical drainage pathways for the different locations of cutaneous head and neck melanomas.\cite{51} Their findings determined the extent of therapeutic neck dissections in melanoma patients with a cervical lymph node metastasis. \cite{52,53} Their lymphatic drainage scheme is mainly based on a hypothetical watershed line,
differentiating anterior lymphatic drainage from posterior drainage. In case a melanoma is located in front of this watershed line a therapeutic neck dissection of the levels I-IV or level I-III with a parotidectomy is advised for patient with an N+ neck. In case a melanoma is located posterior of this watershed line a therapeutic neck dissection of levels II-V is recommended. A modified radical neck dissection with a parotidectomy is advised in case a melanoma is located on the watershed line and a selective neck dissection of the levels III-V in case a melanoma is located in the lower neck (Figure 3). O’Brien’s recommendations are now partly incorporated in the current neck dissection protocol at The Netherlands Cancer Institute. As patients are exposed to the significant morbidity of completion neck dissection, a more selective approach without reduction of survival is desirable.[54,55]

![Figure 3](image-url)
OUTLINE OF THIS THESIS

Evaluation of sentinel node procedures in melanoma surgery
The first part of this thesis focuses on the evaluation of some controversial issues concerning the sentinel node procedure in melanoma patients. Previous publications suggested that early lymph node dissection for a tumour-positive sentinel node could contribute to the entrapment of melanoma cells in lymphatic ducts and thus predispose for the development of in-transit metastases. In chapter two, the incidence of in-transit metastases and other locoregional recurrences is described in patients with an involved sentinel node who underwent early completion lymph node dissection. This incidence is compared to patients who received regional lymph node dissection for palpable nodal disease.

It is not well known that the false-negative rate of sentinel node biopsy is remarkably high even in renowned melanoma centres. The rate of false-negative procedures and their cause at our institute are the subject of chapter three and in chapter four the possible causes for these false-negative procedures are further discussed.

The recently introduced hybrid single photon emission computed tomography camera with integrated radiographic computed tomography (SPECT/CT) could be of additional value in decreasing the number of false-negative procedures. The additional value of SPECT/CT in unselected melanoma patients is analysed, regardless of the location of the primary melanoma or the ease of interpretation of the conventional lymphoscintigram in chapter five.

In a previous study with a median follow up duration of 33 months we described that patients with a minimally involved sentinel node in whom a completion lymph node dissection was omitted did not recur in that basin. Chapter six describes how these very patients fared with a median follow up of five years.

Head and neck lymph node drainage
The second part of this thesis focuses on cervical lymph node drainage in melanoma patients and the assessment of our current neck dissection protocol for patients with an involved sentinel node. Chapter seven addresses the lymphatic drainage patterns of 65 patients with such a melanoma and the implications for a subsequent neck dissection in case an involved cervical sentinel node is found.

Little is known about the precise location, number, size and depth of the suboccipital lymph nodes. Chapter eight presents an anatomic study of this particular region. Because a melanoma on the trunk with a cervical sentinel lymph node is uncommon, three patients with
a melanoma located over the manubrium sterni and drainage to cervical lymph nodes are presented in chapter nine. Following this case series, thirty-nine patients with a melanoma on the shoulder or trunk with lymphatic drainage to the neck were investigated. Their drainage patterns and implications for therapeutic neck dissection are discussed in chapter ten.

This thesis ends with a summary and main conclusions in English, Dutch and Spanish.
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