Results, morbidity, and quality of life of melanoma patients undergoing sentinel lymph node staging
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General introduction and outline of the thesis
INTRODUCTION

Incidence

The melanoma incidence is rising worldwide during the past several decades. This has led to the widely published and debated concept of a melanoma epidemic. According to the World Health Organization, the incidence of melanoma is increasing faster than any other cancer in the world: incidence projections for 2008 place melanoma as the sixth most common malignancy in men and the seventh in women.1 Recently published data from the American Cancer Society estimates the number of new cancer cases and deaths expected in the United States in the year 2010. According to this study, incidence projections place melanoma even as the fifth most common malignancy in men and the seventh in women.2 In the Netherlands, the number of skin cancer patients continues to increase rapidly as well.3 The latest European Standardized incidence Rate (ESR) for invasive melanoma is 20.3/100,000 in males and 27.1/100,000 in females.4 Nowadays, each year more than 4000 patients are diagnosed with melanoma and this disease is the cause of death in almost 700 patients per year. One in 6 Dutch people will develop skin cancer in their lifetime and 1 in 52 will develop melanoma. The absolute total number of new cases with melanoma is expected to be already more than 4800 in 2013; an increase of almost 100% compared to the 2463 new cases in 2000.5 Patients with melanoma have an unpredictable and unimaginable disease. Most of the patients with melanoma present with a stage I or II disease. Fortunately, 43% of the patients with stage I and II disease present with melanomas < 1.0 mm.6 Unfortunately 18.9% of stage I and II patients will develop, in the course of the disease, a local, in-transit, regional, and/or distant failure.7

History of melanoma treatment

The treatment of stage I/II melanoma seems obvious. Guidelines for the treatment of primary melanoma considering excision margins are well defined and widely accepted.8 The therapeutic re-excision is defined with margins of 1 cm in lesions < 2.0 mm Breslow thickness and margins of 2 cm in lesions with > 2.0 mm thickness. However, local recurrences or in-transit metastases (ITM) probably develop in 3-5% of patients.9 ITM and the majority of the local recurrences are part of the same disease process: lymphatic dissemination.10 These types of recurrences are difficult to treat. Prophylactic hyperthermic isolated limb perfusion (ILP) with melphalan showed a trend for a longer disease-free interval after ILP. The impact of ILP was clearly on the occurrence - as first site of progression - of ITM, which were reduced from 6.6% to 3.3%, and of regional lymph node metastases, with a reduction from 16.7% to 12.6%. There was no benefit from ILP in terms of time to distant metastasis or survival and that is why it is not recommended prophylactically.11 Lymph node metastases are rare in patients when the melanoma is < 1 mm. Metastases to regional nodes develop in 15 to 20% of patients with clinically localized melanoma of intermediate thickness. When the lesion is exceeding 4 mm, distant metastases are
frequently present. The survival for patients with clinically palpable regional lymph node metastases depends on the substages of stage III disease; the five-year survival rates are 78%, 59%, and 40% for patients with stage IIIA, IIIB, and IIIC melanoma respectively.6 The majority of patients with stage IV disease die within one year, although a small proportion of patients may benefit from complete metastasectomy and their 5-year survival can be prolonged.12

Since metastasis to a regional node is the most important prognostic factor in early-stage melanoma,6,13 immediate lymph node dissection has been advocated to improve melanoma staging and survival.14 The utility of elective lymph node dissection (ELND) was questioned because only 20% of patients with clinically localized melanoma have occult nodal disease and therefore might benefit from regional lymphadenectomy; the remaining 80% do not need nodal surgery because they have no nodal metastasis.15 Three randomized studies have shown no survival benefit from ELND in patients with stage I/II melanoma16-18, although Balch et al. reported that certain subsets of patients appeared to benefit.14 Since there was no reliable noninvasive means to predict which patients would have nodal disease, the substantial morbidity of ELND (e.g., lymphedema, seroma, and wound infections) had to be balanced against its potential staging value and uncertain survival advantage.19

The development of the sentinel lymph node biopsy (SLNB) concept
In the early nineties Morton introduced the SLNB for patients with primary cutaneous melanoma with stage I/II.20 His hypothesis was a modification of the sentinel lymph node (SLN) concept that Cabanas originally proposed for the management of patients with penile cancer in 1977.21 Morton’s goal was to improve the disease management of the patient whose lymph nodes were negative on clinical assessment. The technique for lymphatic mapping and sentinel node biopsy was developed as a minimally invasive surgical alternative to ELND, a procedure that exposes patients to complications.

The preclinical and clinical development of intraoperative mapping relied solely on vital dyes to identify the SLNs. At the time of surgery, blue dye was injected intradermally at the primary site, an incision was made over the regional nodal basin identified by lymphoscintigraphy, and skin flaps were raised toward the primary site to identify the blue-stained lymphatic channel. The blue lymphatic channel was then traced by meticulous dissection to the blue-stained SLN, which was excised. In this initial study by Morton, all patients underwent completion lymph node dissection (CLND) of the melanoma-draining basin, regardless of the status of the SLN. To facilitate identification of the SLN, Morton et al. incorporated a second mapping agent into intraoperative procedure. SLNs were identified by blue dye staining and/or by radioactive counts measured by a hand-held gamma probe. Because the gamma probe could be used to guide dissection, dual-agent mapping improved the SLN identification rate. It also eliminated the need for dissection of subcutaneous flaps. Initially the radiotracer was injected in the operating room, at the same time as the blue dye,
but the procedure was simplified subsequently by injecting the radiotracer in the nuclear medicine department a few hours before the operative procedure.\textsuperscript{22}

The technique of SLNB in staging melanoma patients was introduced in the Netherlands by Meijer (VU University Medical Center, Amsterdam), shortly afterwards followed by Schraffordt Koops and Hoekstra (University Medical Center Groningen) and Kroon and Nieweg (Antoni van Leeuwenhoek Hospital, Amsterdam).\textsuperscript{23} The purpose of lymphatic mapping in melanoma is to provide node-positive patients with early therapeutic lymph node dissection and perhaps adjuvant systemic therapy. Morton started his first Multicenter Selective Lymphadenectomy Trial (MSLT-I) on January 4, 1994.\textsuperscript{24} The aim of this trial was to study the usefulness of the SLNB in the identification of patients with clinically occult nodal metastases and to evaluate the clinical effect of immediate CLND. In 1995, as a participant in the MSLT-I, the SLNB was launched at the University Medical Center Groningen by Schraffordt Koops and Hoekstra in patients with melanoma and shortly afterwards also in patients with breast cancer.

\textit{Technique}

The SLNB procedure at our institution has been described in detail previously by Doting and outlined in her thesis ‘Sentinel lymph node biopsy in breast cancer and melanoma’.\textsuperscript{25} Patients were admitted to the hospital to undergo the SLNB, reexcision of scar tissue, and if indicated, a CLND. The procedure was performed by a combination of lymphoscintigraphy, patent blue dye and a gamma ray detection. Excision specimens were sent for routine histopathological analysis with haematoxylin-eosin (HE) staining. Specific immunohistochemical staining was performed on HE-negative specimens for the protein S100, the melanoma-associated monoclonal antibody HMB45 and antibodies targeted to the MART-1/Melan-A antigen on melanoma cells. If histopathological examination of the sentinel lymph node revealed metastatic melanoma tissue, then all those patients were advised to undergo CLND of the involved regional lymph node basin. However, since mid-2005 the UMCG participates in the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), which randomizes patients between CLND or nodal observation by ultrasonography of the involved nodal basin in case of a tumor-positive SLN.\textsuperscript{26}

\textit{Staging procedure}

The SLNB represents a valuable staging procedure in patients with cutaneous melanoma.\textsuperscript{27} The question whether SLNB in patients with cutaneous melanoma improves overall survival and disease-specific survival, will hopefully be answered shortly. However, the results of the third planned interim analysis have shown that survival of node positive patients can be prolonged by immediate lymphadenectomy.\textsuperscript{28} The fourth interim analysis, which was
recently performed, might be available in early 2011. Hopefully this will show a survival advantage of SLNB staging and treatment in intermediate thickness melanoma.

*Morbidity*

CLND carries significant risk of both acute and chronic morbidity that may result in increased suffering, decreased function and quality of life. However, the SLNB is a well-established, minimally invasive technique, but is this really the case? The sentinel node procedure appears to have been widely adopted for its prognostic information and its use as a selection criterion for adjuvant systemic therapy trials. These legitimate reasons must be weighed against the disadvantages of general anaesthesia, prolonged operation time, higher costs, postoperative complications, and false-negative rates.

*Aim and outline of this thesis*

The aim of this thesis is to evaluate the short-term and long-term results, as well as side-effects of the SLNB in patients with a primary cutaneous melanoma. Special attention was given to the acute and chronic morbidity of the minimal staging procedure and, if indicated, CLND and to the aspects of quality of life of melanoma patients who had undergone a SLNB with or without CLND.

Chapter 2 starts with a descriptive follow-up study of the first 300 patients with cutaneous melanoma who underwent SLNB. The prognostic value and the disadvantages, such as complication rates, false-negative rates, and the incidence of in-transit metastases, are being discussed. The acute and chronic morbidity of the upper and lower extremities after SLNB in the axilla or groin is described in chapter 3 and 4. The quality of life after axillary or inguinal sentinel lymph node biopsy was measured and compared with the normal population. Quality of life was also compared between the SLNB group and the SLNB + CLND group. It was hypothesized that patients who underwent CLND (especially groin dissection) have more quality of life related problems than patients with SLNB alone. The results of the study are described in chapter 5. The short-term outcome of SLNB was described in chapter 2 while chapter 6 is focused on the long-term follow-up of the SLNB in patients with melanoma. Finally, in the last chapters, all results mentioned in this thesis are summarized. Furthermore, a general conclusion, future perspectives, and recommendations for further research are given.
REFERENCES


