Summary
Samenvatting
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The incidence of cutaneous melanoma is rising worldwide. The rising incidence is mainly due to increasing numbers of thin melanomas. Consequently, an ever-increasing number of patients are in need of follow-up, which is an enormous burden for health care systems.

In this thesis, the main focus is on follow-up of cutaneous melanoma patients, in order to introduce evidence based follow-up schedules. Additionally, primary melanoma staging was investigated, specifically tumour mitotic rate, as well as several aspects of staging of patients with metastatic melanoma.

Part I: Follow-up of melanoma patients

Chapter 1 is a review of the literature regarding the follow-up of melanoma patients. The aim of this chapter was to discuss frequency and duration of follow-up; the clinical background of the health professional involved; optimal intensity of routine investigation; and patient satisfaction with follow-up. The literature review showed that follow-up recommendations varied widely for different tumour thicknesses and American Joint Committee on Cancer (AJCC) Staging. Most authors do not support high intensity routine follow-up investigations. Despite variation in physicians’ recommendation for follow-up investigations, only medical history and physical examination seem to be cost-effective. Lymph node sonography seems to be a promising investigation, although a survival benefit for this test remains to be proven. Anxiety was found in relation to follow-up visits, although previous research indicated that the supply of information to patients during follow-up was much appreciated. Literature on follow-up of cutaneous melanoma patients is mainly retrospective and descriptive. Recommendations can be given only with a low level of evidence. Overall, the existing literature did not support intensive follow-up.

In Chapter 2 the detection of recurrences in patients with cutaneous melanoma treated at the Sydney Melanoma Unit in Australia was investigated. In a prospective study the frequency of detection of the primary melanoma and first melanoma recurrence by patient or doctor was analysed using logistic regression. There was no significant survival difference between patient-detected and doctor-detected first melanoma recurrences. Three-quarters of first melanoma recurrences were detected by patients or their partners and it should be possible to improve this rate even further by better education. More frequent follow-up visits are thus unlikely to be valuable, whereas reductions in follow-up frequency may be safe and economically responsible.
In Chapter 3 the detection of first melanoma recurrence in patients treated at the University Medical Center Groningen was reported and compared to the Australian study. Patients with a first recurrence melanoma of an AJCC Stage I-III primary melanoma were interviewed, to determine how many of them had detected the recurrence themselves. As in the Australian study, three quarters of the first recurrences of melanomas were detected by patients themselves of which only 11% due to structured self-examination. It is not likely that frequent follow-up visits are contributing to the detection of recurrences.

Chapter 4 presents a study on the detection of first and second primary melanomas.

The aim of this study was to assess patient detection of both first primary melanomas and second primary melanomas. It was found that a history of melanoma does not increase the ability of patients to detect new primary melanomas themselves. Physicians are more likely to detect thinner second primary melanomas and those in sites that are poorly visible to patients. It can be concluded that patients who have had a previous melanoma are likely to benefit from regular clinical review by clinicians, who play an important role in the detection of new melanomas.

The study in Chapter 5 aimed to calculate recurrence rates and establish prognostic factors for recurrence in order to produce evidence-based follow-up guidelines. Data were retrieved from the Sydney Melanoma Unit database. Prognostic factors were calculated using the Cox Proportional Hazard Model. Recurrence occurred in 18.9% (895/4726) of patients overall, AJCC Ia 5.2% (95/1822), Ib 18.4% (264/1436), Ila 28.9% (215/750), Iib 41.0% (213/524) and Ilc 45.2% (86/194). In the first two years after diagnosis the proportion of patients developing a recurrence was less than 5% per year for those presenting with Stage I disease and varied between 6.4 and 18.4% per year for Stage II patients. Primary tumour thickness, ulceration and mitotic rate were the most important predictors of recurrence. Based on the findings of this study, a follow-up schedule was proposed: Stage I annually, Stage Ila patients every 6 months for two years and then annually, and Stage Ilb-Ilc patients every 4 months for two years, every 6 months in the third year and annually thereafter.

In Chapter 6 a study was presented in which factors influencing outcome after the development of a first relapse were analysed. A total of 873 patients of the Sydney Melanoma Unit with melanoma relapse were studied. Independent prognostic factors for survival of 481 patients with only loco-regional recurrence were found to be the type of recurrence, primary tumour ulceration and patient age. Predictors for longer survival in 392 patients with distant metastasis at the time of first presentation with recurrence were lung versus other sites, and diagnosis of relapse after 1980 compared with diagnosis before 1980. The results of this study
suggest that management of distant metastases may have improved over the last 25 years, but improved staging techniques make assessment of this unreliable.

**Part II : Primary melanoma staging**

In Part II of the thesis the staging of primary cutaneous melanomas was studied, in particular the value of tumour mitotic rate. In Chapter 7 a study was described regarding the method of assessment and prognostic value of tumour mitotic rate. Data from a large cohort of patients were reassessed in grades I, II or III (mitoses counted per high power field), according to the recommendations of the VIIIth International Pigment Cell Conference, held in Sydney in 1972 under the auspices of the International Union Against Cancer. Tumour mitotic rate was confirmed to be an important independent predictor of survival in patients with primary cutaneous melanoma. However, its predictive value was less than it was when assessed according to the 1982 revisions of the 1972 tumour mitotic rate recommendations; assessment of mitoses per mm$^2$.

**Part III: Metastatic Melanoma Staging**

In the last part of this thesis several aspects of the staging of metastatic melanoma were studied. Chapter 8 describes a population of patients with potential spinal cord compression from metastatic melanoma. The aim of this study was to assess the value of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in demonstrating spinal cord compression by otherwise unsuspected metastatic disease. It was found that FDG-PET can detect imminent, unsuspected spinal cord compression in patients with metastatic melanoma. Immediate anatomical imaging of the spine is recommended in patients who have evidence of spinal cord compression on FDG-PET.

Chapter 9 is focused on the staging of patients with uveal melanoma. Though FDG-PET is of proven value in the detection of metastases in patients with cutaneous melanoma, it has not been investigated before in patients with uveal melanoma. Uveal melanoma is known to metastasise to the liver primarily, often as an isolated presentation of metastatic disease. In this chapter the results of FDG-PET in patients with uveal melanoma were evaluated. FDG-PET is a valuable investigation for the detection of liver metastases in uveal melanoma patients. It appears to be particularly useful in the detection of isolated liver metastases that are potentially resectable.