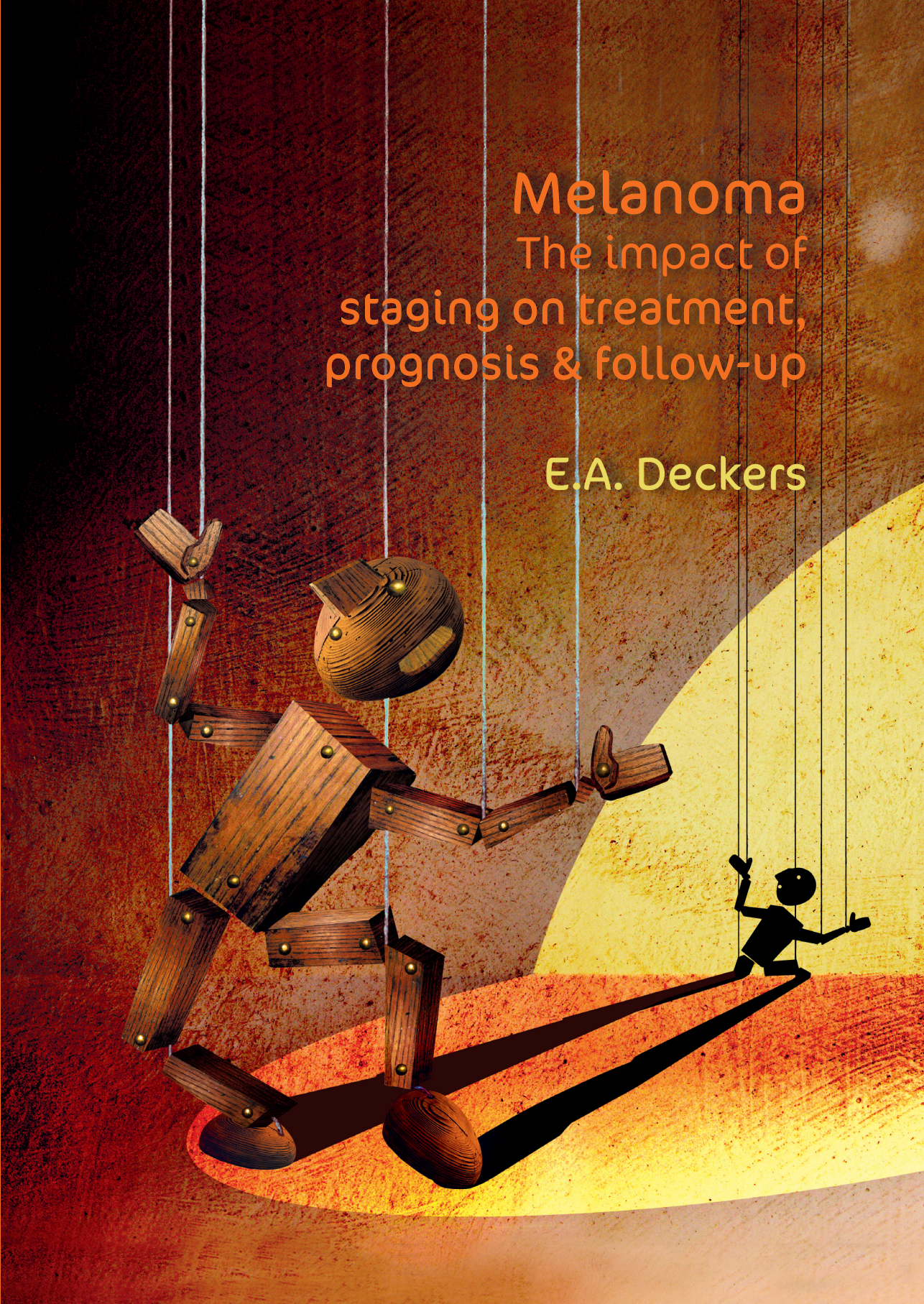
Melanoma
The impact of staging on treatment, prognosis & follow-up

E.A. Deckers



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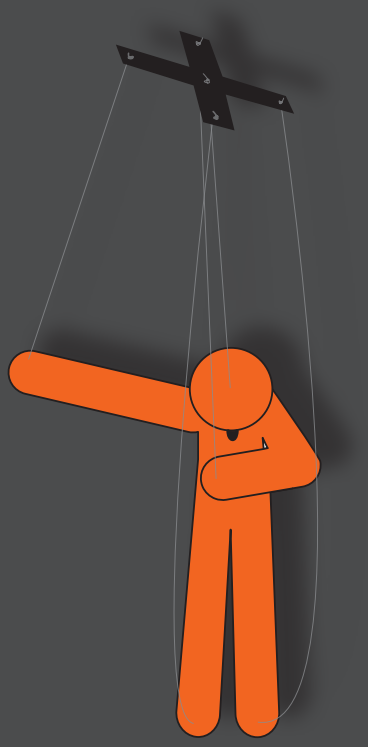

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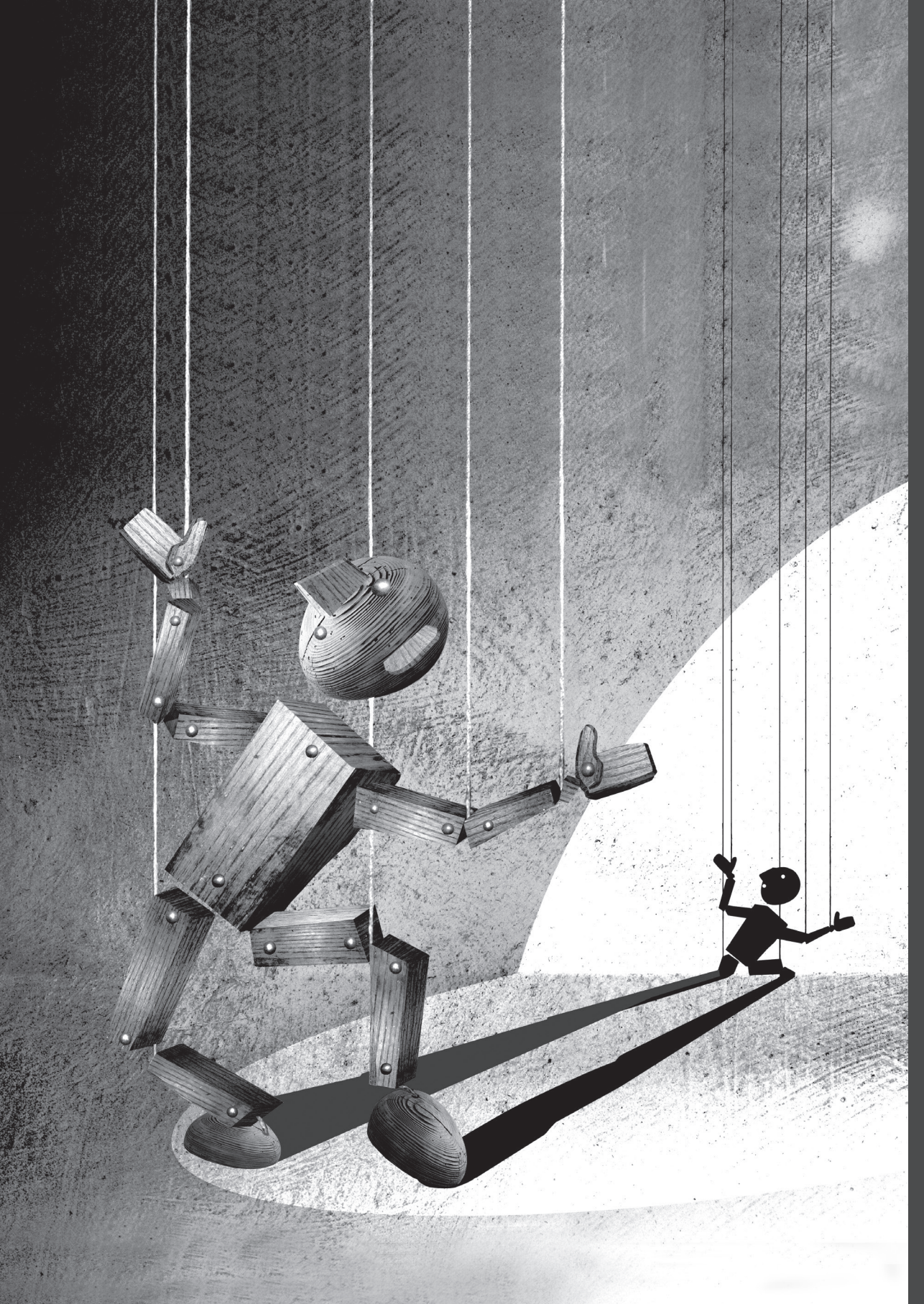
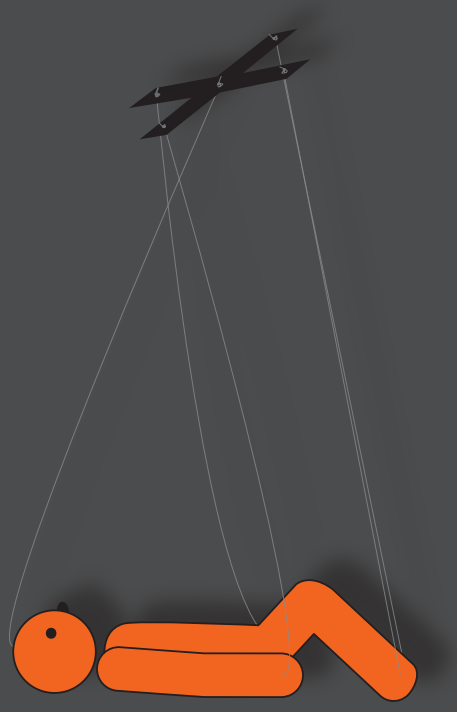


1 General introduction



Incidence

The incidence of melanoma in the Netherlands continues to increase both in men and women. A recent European study showed a statistically significant increase in invasive melanomas (average annual relative change 4% in men and 3% in women) as well as in melanoma in situ (average annual relative change 8% in men and 6% in women). This increase is largely attributable to thin melanomas (average annual relative change of 10% in men and 8.3% in women). The incidence of thick melanomas is also showing an increase, albeit less pronounced. In the Netherlands, the proportion of stage I melanoma at diagnosis is currently 70%.[1,2] In 2018, 7,000 new cases were diagnosed, and 796 persons died as a consequence of the disease.[3] Increased incidence, earlier diagnosis and improved therapeutic options with targeted therapy and/or immunotherapy have contributed to a considerable increase in the prevalence of melanoma.[4] The number of persons diagnosed with melanoma in February 2019 in the Netherlands was approximately 45,600 – in the United States it was more than 1 million.[1,5]

Prevention

The preferred strategy is always to prevent melanoma from developing. That is currently possible only in the form of *education and prevention*. The government, medical insurance companies, the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland), the Dutch Cancer Society (KWF Kankerbestrijding), and the Melanoma Foundation (Stichting Melanoom) all have important roles in this respect. Repeated, effective public education campaigns are necessary to increase awareness of the risks of developing melanoma through excessive exposure to sunlight and ultraviolet radiation, particularly among young people. There is (European) legislation in place limiting exposure to this radiation in tanning beds. The Netherlands Food and Consumer Product Safety Authority (Nederlandse Voedsel- en Warenautoriteit) has laid down statutory rules for the use of tanning beds in tanning salons ('indoor tanning') with a minimum age of 18 years. This is because early-age sunburn doubles the lifetime risk of developing cutaneous melanoma.[6] It should also be kept in mind that public education campaigns take a very long time to produce positive results. These

campaigns create awareness of the dangers of excessive exposure to sunlight from childhood, the risks of ultraviolet radiation in indoor tanning in relation to the development of skin cancer, and the importance of timely consultation of a general practitioner in case of suspicious skin defects. The campaigns supported by Dutch Cancer Society, such as 'smeren, kleren, weren', have unfortunately not been effective yet in reducing the incidence of melanoma in the Netherlands. In Australia, such preventive campaigns, known as 'slip, slop, slap' (slip on a shirt, slop on the 50+ sunscreen, slap on a hat) have resulted in a reduction in the incidence of melanoma in young people.[7]

Staging

The first TNM classification of melanoma was defined in 1977 by the American Joint Committee on Cancer (AJCC). Over the next four decades, this classification went through seven revisions. The latest edition, the '8th AJCC Edition', is from 2017.[8] Most publications about melanoma are currently still based on the 7th Edition. This dissertation is also based on the 7th AJCC Edition (Figure 1).

The various changes to the AJCC classification over the past four decades were all made on the basis of studies using large international patient databases for melanoma. The most significant changes within the AJCC classification are due to the introduction of mitotic rate, sentinel lymph node biopsy, use of immunohistochemistry in sentinel lymph node diagnostics, and the LDH biomarker.[8,9] In the T category, the thickness of the cutaneous melanoma (Breslow thickness) and tumor ulceration have greater prognostic value than depth of invasion (Clark level) or mitotic index. In the N category, the most important parameters are: number of lymph node metastases, tumor size (microscopic or macroscopic), and the presence in the skin of in-transit metastases, satellites and microsatellites. In the M category, the LDH biomarker was introduced. Figure 2 contains an overview of the current, 8th AJCC melanoma classification.[9] This new classification aims to move from a population-based approach to a more personalized approach, since the increased levels of specification of melanoma stages as well as the development of 'targeted' systemic therapy mean that the earlier 'one size fits all' approaches are now no longer tenable.

FIGURE 1 **AJCC Staging 7th edition**

Anatomic stage/prognostic groups							
Clinical staging				Pathologic staging			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
		--	--		T1-4a	N2a	M0
		--	--	IIIB	T1-4b	N1a	M0
		--	--		T1-4b	N2a	M0
		--	--		T1-4a	N1b	M0
		--	--		T1-4a	N2b	M0
		--	--		T1-4a	N2c	M0
		--	--	IIIC	T1-4b	N1b	M0
		--	--		T1-4b	N2b	M0
		--	--		T1-4b	N2c	M0
		--	--		Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

FIGURE 2 **AJCC Staging 8th edition**

Anatomic stage/prognostic groups							
Clinical staging				Pathologic staging			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	--	--	IB	T1b	--	--
	T2a	--	--		T2a	--	--
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	--	--		T2a	--	--
Stage IIB	T3b	--	--	IIB	T3b	--	--
	T4a	--	--		T4a	--	--
Stage IIC	T4b	--	--	IIC	T4b	--	--
Stage III	Any T	≥ N1	M0	IIIA	T1-2a	N1a	M0
		--	--		T1-2a	N2a	--
		--	--	IIIB	T0	N1b-c	M0
		--	--		T1-2a	N1b-c	--
		--	--		T1-2a	N2b	--
		--	--		T2b-3a	N1a-2b	--
		--	--	IIIC	T0	N2b-c	M0
		--	--		T0	N3b-c	--
		--	--		T1a-3a	N2c-3c	--
		--	--		T3b-4a	Any N	--
		--	--		T4b	N1a-2c	--
		--	--	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

Follow-up

In the Netherlands, the current follow-up strategy for melanoma patients is based on a national guideline and differs depending on stage.[10] The guideline's recommendations mostly aim at stage IB-II patients, since the highest levels of recurrence or additional primary melanoma are seen in this group in the first 2-3 years after diagnosis.[11] It is recommended that these patients should be checked frequently during these first few years. However, studies have shown that such frequent check-ups also have some disadvantages. Patients experience relatively high stress levels around their hospital check-up appointments.[12] An important point to note is that recurrences are mostly detected by patients themselves and/or their partners, and many patients will actively seek treatment when needed, with the consequence that frequent follow-ups are not always preferable.[13,14] In light of this, a recent prospective randomized study undertaken at the UMCG, the 'Melanoma Follow-up Study' (MELFO), has attempted to examine the possibility of implementing a shortened follow-up program for stage IB-II melanoma patients without overlooking any recurrent melanoma. The 1-year outcomes have shown that patients on a reduced stage-adjusted follow-up schedule, compared to patients in the follow-up schedule as recommended by the Dutch guideline, report comparable quality of life and anxiety levels, that recurrences are detected equally often, and that hospital costs are reduced.[15] Longer-term outcomes will be available upon completion of the MELFO study.

Biomarkers

The serum biomarker lactate dehydrogenase (LDH) has a role in diagnosing stage IV melanoma in the 8th edition of the AJCC classification; distant metastases (M) defined by anatomical location of the distant metastasis and LDH by serum level.[9]

The role of the biomarkers S-100 calcium-binding protein B (S-100B) and LDH in the follow-up of melanoma patients is still unclear.[16-18] Not only are the serum levels of these two markers difficult to interpret correctly, but the stage for which they are most suited is also not entirely clear. Both are currently applied mostly in the response evaluations of systemic therapy for stage IV melanoma patients. Efforts

are also underway to find new prognostic, predictive and response biomarkers in order to select patients for specific treatments, to monitor treatment, and to detect non-clinical recurrence, but they have to date been unsuccessful.[19]

Follow-up is still mostly oriented towards symptoms reported by patients as well as imaging results (FDG PET/CT). In some guidelines, e.g. in Switzerland and Germany, S-100B has been assigned a role in follow-up.[20] Because of the difficulties in interpretation of serum levels, this method is still often combined with imaging. The benefits to be had with the use of these biomarkers are the potential to reduce the frequency of imaging, which is often costly. A recently started Swedish study, the TRIM study, a randomized trial to assess the role of imaging (whole-body CT or FDG PET scan) during follow-up after radical surgery of high risk melanoma, investigates the use of S-100B and LDH together with a standard scanning protocol for melanoma patients.[21] This means that scans are made regardless of the presence of complaints and/or increased serum levels. However, such a scanning protocol is associated with a high radiation burden and high costs. It remains to be seen whether this will lead to survival gains.

The successful targeted therapy with BRAF/MEK inhibitors and immunotherapy with checkpoint inhibitors in disseminated melanoma, FDG PET, FDG PET/CT and whole body CT protocols are increasingly being used in the follow-up of high-risk melanoma patients (stage IIC and stage III) to detect recurrences in an early phase. Is it possible to detect these recurrences in high-risk patients earlier with the use of the relatively cheap biomarker S-100B? It is unclear in this context whether these FDG PET, FDG PET/CT and whole-body CT protocols are really justified.

Treatment

The changes that have occurred over the past four decades in the excision margins in the local surgical treatment of melanoma were based mainly on four prospective trials. First, the vertical thickness of the melanoma according to Breslow is determined from the diagnostic excision biopsy. The recommended re-excision margin is 1 cm for tumors <2.0 mm, and 2 cm for tumors >2.0 mm.[22] These excision margins are based on several excision margin studies; however, the relevant evidence is still lacking.[23] The Melanoma Margins Trial (MelmarT trial)

investigating 1cm vs. 2cm wide excision margins for primary cutaneous melanoma is expected to provide the final answer as to whether smaller excision margins are adequate without affecting local recurrence and melanoma-specific survival, and whether this would improve quality of life.[24,25]

In 1992, a concept was developed for minimally invasive regional staging of melanoma patients with stage IB-II using 'sentinel lymph node biopsy' (SLNB). The sentinel lymph node is the first lymph node to which cancer cells will metastasize. A sentinel lymph node biopsy involves injecting a radioactive tracer and a blue dye intradermally and trying to remove this specific lymph node through a minor operation, and examining it for tumor cells.[26] This regional staging of lymph nodes was included in the 7th edition of the AJCC.[9] Sentinel lymph node biopsy has since been the default minimally invasive staging method for patients with stage IB-II melanoma, with minimal treatment morbidity.[27] However, unfortunately, sentinel lymph node procedures have not produced the improved overall survival of melanoma that was expected previously. In case of positive sentinel lymph node biopsy, additional regional lymph node dissection will not lead to improved survival as compared to following a 'wait-and-see policy' and therapeutic lymph node dissection in case of regional recurrence.[28,29] However, the morbidity of a therapeutic lymph node dissection, as in the latter case, is significantly higher.

Positron emission tomography (PET scan) or the serum biomarker S-100B are not useful in staging patients with stage IB-II melanoma. However, high-risk patients can be staged with PET and the biomarker S-100B.[30-32] Until recently, this knowledge had only prognostic value. Over the past decade, great strides have been made in the systemic therapy of regional and distant metastasized melanoma with the emergence of targeted therapy with 'BRAF inhibitors' (dabrafenib and vemurafenib) in BRAF-mutated patients, with MEK inhibitors (trametinib and cobimetinib) and the recently developed effective immunotherapy with the immune checkpoint inhibitors anti CTLA-4 antibodies (ipilimumab) and anti-PD1 antibodies (nivolumab and pembrolizumab).[4] These new systemic therapies have resulted in greatly improved and often enduring disease-free survival in (neo)adjuvant settings with high-risk stage III patients as well as in therapeutic settings with stage IV patients. These novel systemic treatments are very costly, and only 20% of treated patients will ultimately benefit from them. In addition, these treatments have substantial side effects.

Prognosis

The prognosis of patients with melanoma has improved markedly in recent decades. From 2000 to 2005, 5-year survival rates have climbed from 87% to 91%. In the Netherlands, the 3-year survival is currently 100% for patients with a stage I melanoma, 84% with stage II, 69% with stage III and 17% with stage IV.[1] Are there possibilities for further improvements in the prognosis of melanoma?

This is only possible by providing appropriate care to melanoma patients which integrates patient education, treatment and research. A good example is the Melanoma Institute of Australia (MIA), that integrates the different aspects, ranging from prevention to personalized treatment, in a single organization.[33] Another very good example is the multimillion-dollar Melanoma Moon Shot™ program of MD Anderson Cancer Center that receives funding from the Specialized Programs of Research Excellence (SPORE) of the National Cancer Institute. This program focuses on both primary prevention and early diagnosis and personalized melanoma treatment.[34] Preclinical findings are rapidly applied in treatment options for melanoma patients.[35]

For many years now, UMCG has the Groningen Comprehensive Cancer Center, that facilitates a Multidisciplinary Melanoma Treatment Team that provides melanoma patients with fully integrated care, i.e. diagnostics as well as treatment.[36] This is based on advanced diagnostics and treatment procedures aiming at improving the prognosis of melanoma patients. UMCG is one of eight centers treating advanced melanomas in the Netherlands. The UMCG Multidisciplinary Melanoma Treatment Team also provides advice to regional hospitals on behalf of IKNL (Netherlands Comprehensive Cancer Organization).

Costs of care

The prognosis of patients with stage III and IV melanoma could possibly be improved further, but that will certainly lead to increased costs of care. The total healthcare expenditure in the Netherlands will exceed the 100 billion euro mark in 2019 for the first time; it now represent more than 13.3% of the Gross National

Product (GNP).[37] Cancer-related healthcare expenditure in 2011 represented 4.8% of the total healthcare expenditure in the Netherlands. The increase in cancer incidence and prevalence as well as the new treatment options will lead to further increases in expenditure. However, melanoma is a rare form of cancer, and its share in the overall costs of treating cancer is minimal. The annual costs of treating patients with melanoma is still expected to increase by tens of millions of euros. This increase will be due to: 1) the increase in incidence and prevalence of melanoma and associated specialist healthcare, and diagnostics (radiology, nuclear medicine, laboratory) and to 2) the new systemic treatments (targeted therapy and immunotherapy) for melanoma in addition to existing surgical and/or radiation procedures.

Treatment as well as clinical and fundamental scientific melanoma research will need to increase, and should focus on a 'personalized approach' in order to ensure the optimal use of the available means and keeping the costs manageable.[38] The costs may be reduced further by opting for 'value-based melanoma healthcare' that focuses on improving the outcomes of multidisciplinary melanoma treatment and reducing the associated healthcare costs, preferably implemented as a 'Resultaat Verantwoordelijke Eenheid' (RVE) or 'focus clinic' that focuses on providing care to melanoma patients.[38,39] The in June 2019 initiated experiment of healthcare providers and pharmaceutical companies with a new payment scheme for costly cancer medication is a step towards a 'no cure, no pay' culture in healthcare. In that case, medication will be paid only if there is a positive response at 16 weeks from the start of treatment. It is hoped that this allows costly medicines to remain available and that physicians can still prescribe them to post-treatment (melanoma) patients who may benefit.[40]

Research questions

The focus of melanoma research activities within the Division of Surgical Oncology during the past decades was mainly on the options for using adjuvant and therapeutic regional limb perfusion in patients with cutaneous melanoma. This was followed by assessments of the options for using novel, non-invasive and minimally invasive diagnostics for melanoma staging with Positron Emission Tomography (PET) scans, sentinel lymph node biopsy (SLNB), and the biomarker S-100B.

Building on the insights gained from recent studies and the demand for more personalized melanoma treatment as described above, the following research questions will be examined in the present thesis,

1) Is a reduction in follow-up frequency for patients with stage IB-II melanoma possible without affecting quality of life, number of recurrences, and melanoma-specific and overall survival?
2) What is the current role of minimally invasive staging with sentinel lymph node biopsy?
3) Does Body Mass Index of patients with stage IB-II melanoma affect recurrence free period and melanoma-specific and overall survival?
4) Is S-100B an extra selection tool for FDG PET/CT scanning in the follow-up of AJCC Stage III melanoma patients?
5) Is there a correlation between the serum level of the biomarker S-100B and the SUV uptake of a FDG-PET scan in disseminated melanoma?

The above research questions will be answered in chapters II to VI. This is followed by a summary in English and Dutch in chapters VII and VIII. Lastly, developments in the diagnostics and treatment of melanoma will be highlighted in chapter IX, 'Future perspectives'.

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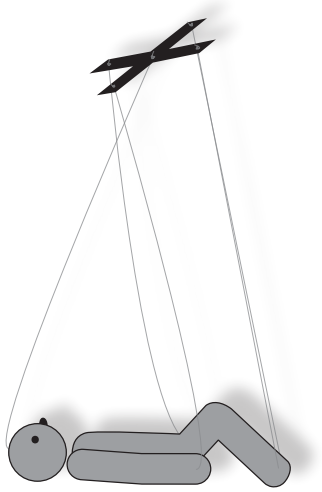
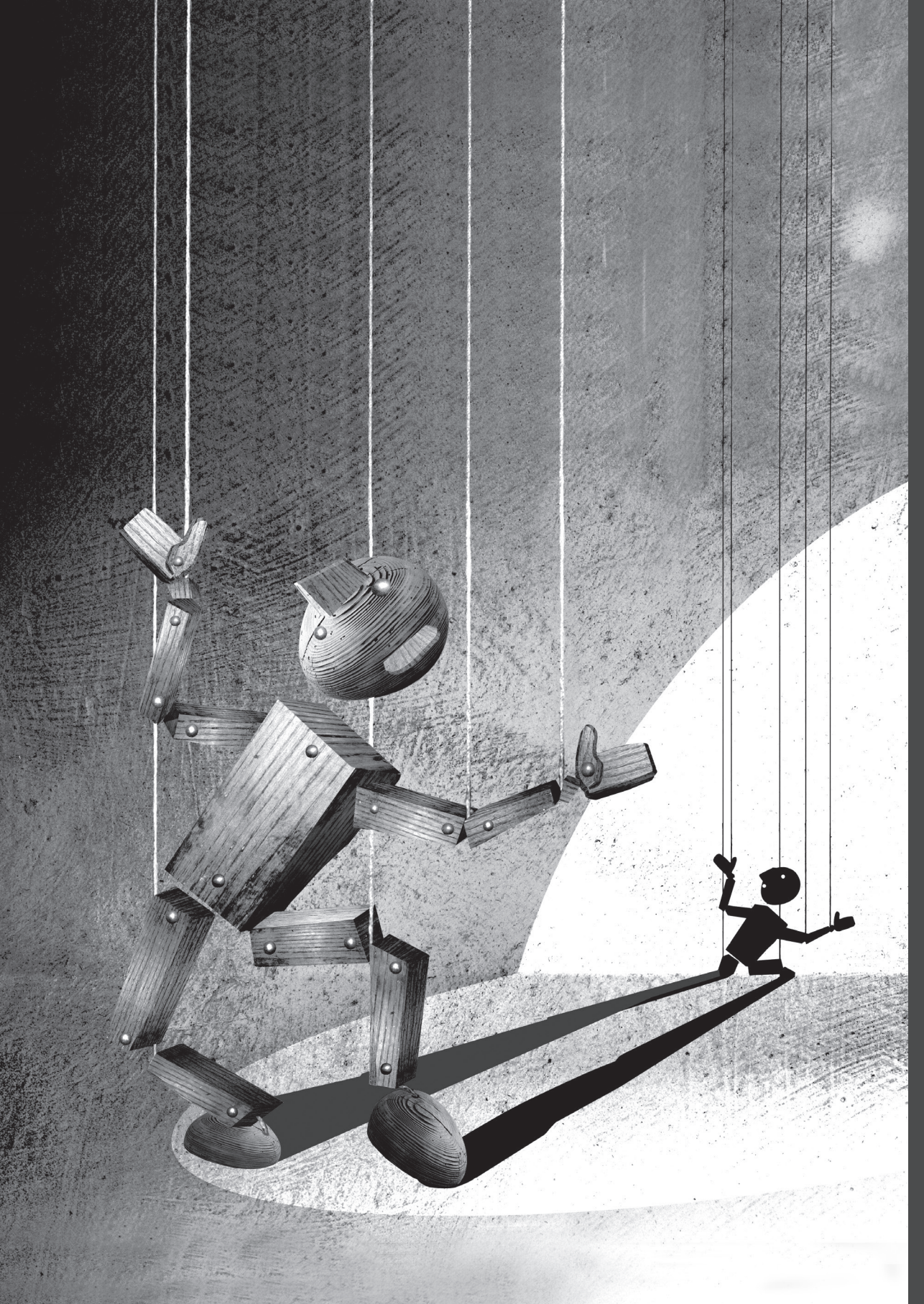
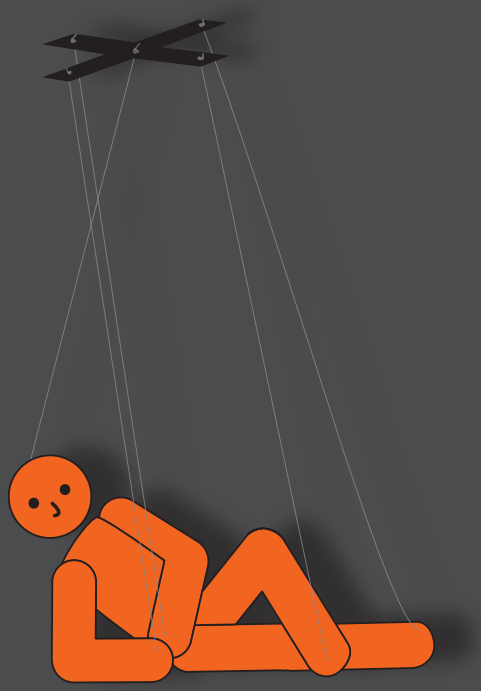




2A

The MELFO-Study: a multi-center prospective randomized clinical trial on the effects of a reduced stage-adjusted follow-up schedule on cutaneous melanoma IB-IIC patients - results after 3-years



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Abstract

Background
This study compares well-being, recurrences, and deaths of early-stage cutaneous melanoma patients in follow-up as recommended in the Dutch guideline with that of patients in a stage-adjusted reduced follow-up schedule, three years after diagnosis, as well as costs.

Methods
One-hundred-eighty eligible pathological AJCC-stage IB-IIC, sentinel node staged, melanoma patients (response=87%, 48%=male, median age=57 years), randomized into a conventional (CSG: n=93) or experimental follow-up schedule group (ESG: n=87), completed Patient-Reported Outcome Measures (PROMs) at diagnosis (T1): State-Trait Anxiety Inventory (STAI-s), Cancer Worry Scale (CWS), Impact of Event Scale (IES), RAND-36 (Mental and Physical Component scales (PCS/MCS)). Three years later (T3), 110 patients (CSG: n=56, ESG: n=54) completed PROMs, 42 declined (23%).

Results
Repeated measures ANOVAs showed a significant group effect on the IES (p=0.001) in favor of the ESG, and on the RAND-36 PCS (p=0.02) favoring the CSG. Mean IES and CWS scores decreased significantly over time, those on the RAND-36 MCS and PCS increased. Effect sizes were small. Twenty-five patients developed a recurrence or second primary melanoma; of whom thirteen patients died within three years. *Cox proportional-hazards models* showed no differences between groups in recurrence free survival (HR=0.71(0.32-1.58), p=0.400) and disease free survival (HR=1.24(0.42-3.71), p=0.690). Costs per patient after three years (computed for 77,3% of patients) were 39% lower in the ESG.

Conclusion
These results seemingly support the notion that a stage-adjusted reduced follow-up schedule forms an appropriate, safe, and cost-effective alternative for pathological AJCC-stage IB-IIC melanoma patients to the follow-up regime as advised in the current melanoma guideline.

Background

The worldwide incidence of cutaneous melanoma increased over the past decade.[1] In the Netherlands, the incidence of melanoma quadrupled between 1990 and 2018 from 1561 to 7046 new cases.[2] However, increase in mortality was lower. The rate doubled between 1990 and 2010 from 348 to 783 cases, after which it stabilized. In 2017, 796 patients died of melanoma.[3] Consequently, the prevalence of melanoma is increasing in the Netherlands.

Increasing prevalence results in a growing number of patients in follow-up. Most guidelines regarding follow-up schedules recommend at least a five, 10-year, or lifelong surveillance, which makes melanoma follow-up a burden in both time and financial costs.[4,5] Additionally, patients are exposed to many outpatient clinic or general practitioner (GP) visits, which may result in emotional stress.[5-7]

Most of the recommendations in the current guidelines are based on recurrence risk, early detection and consequently improved survival.[8-12] Almost 90% of the recurrences occur in the first three years after primary diagnosis.[4,9,12-14] Patients with a higher stage at primary diagnosis have a higher risk of recurrence and the risk of recurrence after 10 years follow-up is low (2.4%).[6,7,10,15]

The lack of consensus in guidelines regarding the follow-up of cutaneous melanoma patients was the reason to initiate the melanoma follow-up study (MELFO). Preliminary one-year results showed that a stage-adjusted, reduced follow-up schedule neither adversely affected patients' well-being nor the number of recurrences or melanoma deaths, and that financial costs were lower compared with the conventional follow-up schedule recommended in the Dutch guideline.[16]

The aims of the present study were to examine comparability in (1) well-being and (2) the number and time of recurrences and deaths of early-staged melanoma patients who were subjected to the follow-up schedule advised in the Dutch guideline and patients who received a stage-adjusted reduced follow-up schedule, three years after diagnosis. The hypotheses were that there would be no differences between the two groups in these outcomes and (3) that costs would be lower when patients were followed-up less frequently.

Methods

Study design

Detailed methods of this multicenter, randomized clinical trial (NCT0108004), initiated by the Department of Surgical Oncology of the University Medical Center of Groningen (UMCG), have been described previously.[16] Participants were randomized into two groups: one following the conventional schedule recommended in the Dutch Melanoma guideline, and one whose follow-up was a stage-adjusted reduced schedule (Table 1). The primary endpoint was patients' well-being. Secondary endpoints were recurrences, melanoma-related deaths, and costs.[16]

Patients and procedure

Inclusion criteria were sentinel lymph node negative melanoma patients, pathological American Joint on Cancer Committee (AJCC) stage IB-IIC, who had undergone surgery with a curative intent between 2006 and 2013. Patients aged<18 or >85 years, those not mastering the Dutch language sufficiently, and those who had another malignancy were excluded.

TABLE 1 **Frequency of follow-up visits for the conventional follow-up schedule, as recommended by the Dutch Melanoma guideline, and a reduced and stage-adjusted experimental follow-up schedule[16]**

Conventional follow-up schedule

Years*	1	2	3	4	5	6-10
AJCC stage						
IB	4	3	2	2	2	
IIA	4	3	2	2	2	1
IIB	4	3	2	2	2	1
IIC	4	3	2	2	2	1

Experimental follow-up schedule

Years*	1	2	3	4	5	6-10
AJCC stage						
IB	1	1	1	1	1	1
IIA	2	2	1	1	1	1
IIB	3	3	2	1	1	1
IIC	3	3	2	1	1	1

AJCC American Joint Committee on Cancer, 7th edition
*Year after surgery for primary melanoma

Eligible patients were randomized into the conventional (CSG) or experimental schedule group (ESG) after giving informed consent. The Netherlands Comprehensive Cancer Organization (IKNL) performed randomization and data management. Patients completed questionnaires at study entry which was shortly after diagnosis (T1), and one (T2) and three years later (T3). Patients were excluded from T2 or T3 in case of a recurrence, a second primary or when they had died. Clinicians provided follow-up information on all patients included at T1 during the three years of the study[16] or until patients developed a recurrence, a second primary, or died. The present study focused on T1 and T3.
The study was approved by the medical ethics committee of the UMCG (METc2004.127).

Instruments

Patients answered questions on gender, age, level of education, relationship status, daily activities, and co-morbidities at T1. They answered questions on schedule satisfaction, frequency of self-inspection, and the number of melanoma-related GP visits at T1 and T3. Medical specialists gave diagnostic (primary melanoma site, Breslow thickness, ulceration, AJCC classification) and follow-up information (date of every outpatient visit, date and location of recurrence, date and cause of death). Patients completed the following patient-reported outcome measures (PROMs) at T1 and T3:

(1) The State-Trait Anxiety Inventory-state version (STAI-S), a 20-item questionnaire measuring the transitory emotional condition of stress or tension perceived by the patient. Items could be scored on a 4-point scale ranging from 'not at all'=(1) to 'very much'=(4) (range 20-80).[17]
(2) The 3-item Cancer Worry Scale (CWS) measuring concerns about developing cancer again and the impact on daily activities.[18-20] Higher scores mean more worries (range 3-12).
(3) The 15-item Impact of Event Scale (IES) evaluating the extent to which patients suffer from life-hazards, in this case of having a melanoma, in terms of avoidance and intrusion.[21,22] A higher score (range 0-75) corresponds to a higher level of stress response symptoms (SRS).
(4) The RAND-36, a 36-item health-related quality of life questionnaire, of which the mental component (MCS) and physical component summary scores (PCS) were used. The summary scores are standardized with a mean of 50 and a standard deviation of 10.[23]

Total melanoma-related hospital costs were calculated for 51 patients of a University Medical Center (Groningen) and for 34 patients of a large teaching hospital (Isala Clinics, Zwolle) participating at T3 (representing 77,3% of participants). Costs per melanoma patient are considered largely comparable between hospitals as a consequence of the financing system in the Netherlands which is a price competitive reimbursement system. Costs per patient are calculated using diagnosis-treatment combinations (DBCs). DBCs are developed for a combination of interventions and treatments that belong to a certain diagnosis.[24] These DBCs are fixed prices and are based on agreement between hospitals and health insurance companies. Costs taken into account included all follow-up visits and telephone consultations, and detection and treatment of recurrences. Expenses for GP consultations were not taken into account.

Statistical analysis

Power analysis performed has been described previously.[16] Statistical analyses were performed using IBM SPSS statistics version 22 (SPSS Inc; Chicago, IL). Patient characteristics were described, and comparisons between study groups were performed using independent T-tests, Mann Whitney U-test, Chi-square tests, or Fisher Exact Tests, as appropriate. Repeated measures ANOVAs were conducted to examine differences between groups, time differences, and interaction effects in PROMs. Effect sizes (ES) were computed to examine clinical relevance when a difference was found to be statistically significant. ES values of ≥0.5 are considered large, those between 0.3 and 0.5 moderate, and those<0.3 small.[25] Cox proportional-hazards models were computed to examine the effect of group on recurrence-free survival (RFS) and disease-free survival (DFS).
P-values<0.05 were considered statistically significant.

Results

Of the eligible 207 patients, 27 refused participation (response=87%).[16] Of the 180 participants at T1, 87 were male (48%); median age was 57 (range 20-85) years. Patients were randomized into a conventional (CSG; n=93) or experimental follow-up schedule group (ESG; n=87). No significant differences between study groups were found in socio-demographic or illness-related characteristics at T1.[16]

At T3, 110 patients completed questionnaires. Of the 70 patients who did not, 28 were excluded (recurrent disease, a second primary or death) and 42 (23%) declined to complete T3 questionnaires (Figure 1). No significant differences were found in socio-demographic and illness-related variables between T3 CSG and ESG participants (Table 2). T3 participants and those who dropped-out were comparable in T1 socio-demographic and illness-related variables, as well as in mean PROMs scores (data not shown).

No significant between group difference was found at T3 in satisfaction with follow-up schedule (p=0.162), nor in reason for dissatisfaction (p=0.444). Adherence with assigned follow-up schedule differed significantly between groups (p=0.031). Significantly more ESG than CSG patients paid more visits to the medical specialist than scheduled. Of the patients who paid extra visits, 16 (64%) paid only one extra visit during the three years. Medians for the number of fewer or extra visits did not

FIGURE 1 **Flowchart of inclusion and randomization**

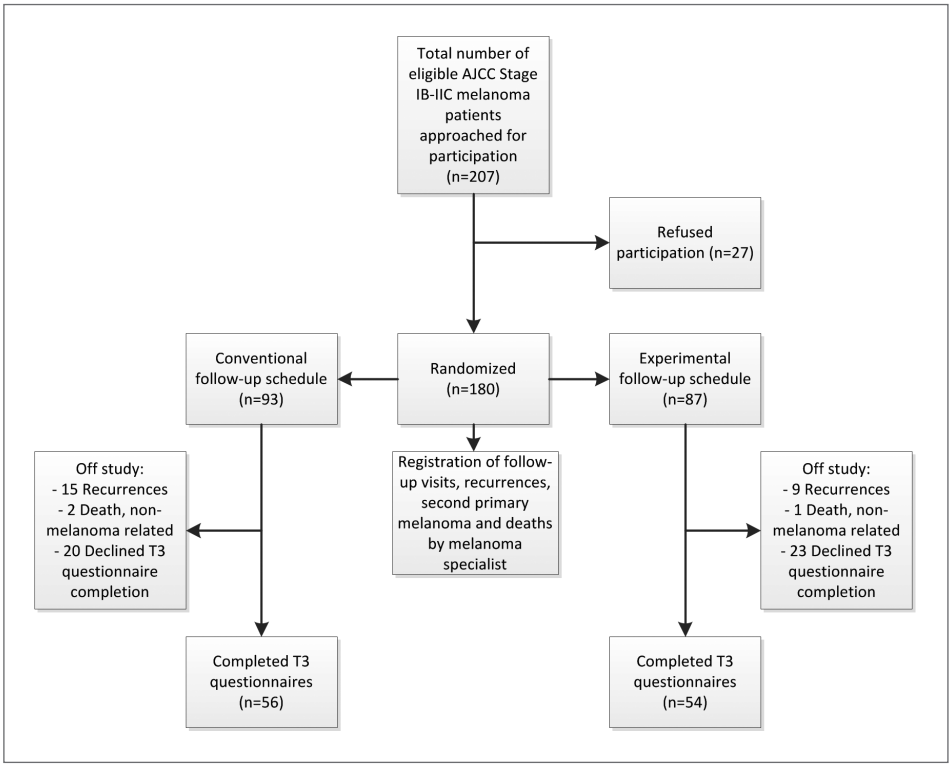

TABLE 2 **Descriptives of sociodemographic and illness-related characteristics at T1, and of follow-up related questions at T3 of the 110 participants at T3, along with comparison between study groups (CSG: n=56, ESG: n=54) at T3**

Characteristics at T1	Total (n=110) N (%)	Conventional schedule (n=56) N (%)	Experimental schedule (n=54) N (%)	*p*-value
Gender				0.181[#]
Female	56 (50.9)	25 (44.6)	31 (57.4)	
Male	54 (49.1)	31 (55.4)	23 (42.6)	
Age (year)				0.161[$]
Mean±SD (range)	56±13 (24-81)	55±14 (26-81)	58±11 (24-78)	
Level of education[a]				0.312[#]
High	44 (40)	24 (42.9)	20 (37.0)	
Intermediate	44 (40)	24 (42.9)	20 (37.0)	
Low	22 (20)	8 (14.2)	14 (26.0)	
Relationship				0.189[#]
With partner	95 (86.4)	46 (82.1)	49 (90.7)	
Without partner	15 (13.6)	10 (17.9)	5 (9.3)	
Daily activities				0.257[#]
Employed for wages	59 (53.6)	33 (58.9)	26 (48.1)	
Not employed for wages	51 (46.4)	23 (41.1)	28 (51.9)	
Presence of co-morbidities				0.053[#]
No	71 (64.5)	41 (73.2)	30 (55.6)	
Yes	39 (35.5)	15 (26.8)	24 (44.4)	
Primary melanoma site				0.463[#]
Lower extremity	32 (29.1)	20 (35.7)	12 (22.2)	
Upper extremity	21 (19.1)	9 (16.1)	12 (22.2)	
Trunk	46 (41.8)	22 (39.3)	24 (44.4)	
Head/neck	11 (10)	5 (8.9)	6 (11.2)	

Characteristics at T1	Total (n=110)	Conventional schedule (n=56)	Experimental schedule (n=54)	*p*-value
	N (%)	N (%)	N (%)	
Breslow thickness (mm)				0.123#
<1.0	8 (7.3)	1 (1.8)	7 (13.0)	
1.00-1.99	63 (57.3)	36 (64.3)	27 (50)	
2.00-3.99	31 (28.2)	15 (26.8)	16 (29.6)	
≥4.00	8 (7.3)	4 (7.1)	4 (7.4)	
Median (range)	1.7 (0.6-8.0)	1.6 (0.9-8.0)	1.7 (0.6-7.3)	
Ulceration				0.215#
No	85 (77.3)	46 (82.1)	39 (72.2)	
Yes	25 (22.7)	10 (17.9)	15 (27.8)	
AJCC classification				0.487#
IB	65 (59.1)	34 (60.7)	31 (57.4)	
IIA	24 (21.8)	14 (25.0)	10 (18.5)	
IIB	15 (13.6)	5 (8.9)	10 (18.5)	
IIC	6 (5.5)	3 (5.4)	3 (5.6)	
Follow-up related questions at T3				
Schedule satisfaction[b]				0.162#
No	9 (8.5)	7 (13)	2 (3.9)	
Yes	96 (91.5)	47 (87)	49 (96.1)	
missing	5	2	3	
Reason dissatisfaction[b]				0.444*
Wish for less visits	4 (44.4)	4 (57.1)		
Wish for more visits	5 (55.6)	3 (42.9)	2 (100)	
Adherence to follow-up schedule				**0.031#**
Less outpatient clinic visits than scheduled	11 (10)	7 (12.5)	4 (7.4)	
1 visit less	*6 (54.5)*	*3 (42.8)*	*3 (75)*	
2 visits less	*3 (27.3)*	*3 (42.8)*		
3-4 visits less	*2 (18.2)*	*1 (14.3)*	*1 (25)*	
median (range)	1 (1-4)	2 (1-4)	1 (1-3)	0.466^

TABLE 2 **Continued**

Characteristics at T1	**Total (n=110)**	**Conventional schedule (n=56)**	**Experimental schedule (n=54)**	***p*-value**
	N (%)	**N (%)**	**N (%)**	
Conform schedule	74 (67)	42 (75)	32 (59.3)	
More outpatient clinic visits than scheduled	25 (23)	7 (12.5)	18 (33.3)	
+1 extra visit	*16 (64)*	*4 (57.1)*	*12 (66.7)*	
+2 extra visits	*5 (20)*	*1 (14.3)*	*4 (22.2)*	
+3-5 extra visits	*4 (16)*	*2 (28.6)*	*2 (11.1)*	
median (range)	1 (1-5)	1 (1-4)	1 (1-5)	0.547^
Melanoma-related GP visits				0.439#
No	27 (24.5)	12 (21.4)	15 (27.8)	
Yes	83 (75.5)	44 (78.6)	39 (72.2)	
Extra GP visits				
+1 visit	*38 (45.8)*	*21 (47.7)*	*17 (43.6)*	
+2 visits	*29 (34.9)*	*17 (38.6)*	*12 (30.8)*	
+3-5 visits	*16 (19.3)*	*6 (13.6)*	*10 (25.7)*	
median (range)	2 (1-5)	2 (1-5)	2 (1-5)	0.425^
Total (hospital+GP) extra visits	87 (79.1)	44 (78.6)	43 (79.6)	0.221*
+1 extra visit	*33 (37.9)*	*18 (40.9)*	*15 (34.9)*	
+2 extra visits	*25 (28.7)*	*16 (36.4)*	*9 (34.9)*	
+3 extra visits	*13 (14.9)*	*4 (9.1)*	*9 (20.9)*	
+4 extra visits	*10 (11.5)*	*3 (6.8)*	*7 (16.3)*	
+5-7 extra visits	*6 (6.9)*	*3 (6.8)*	*3 (7.0)*	
Frequency of self-inspection[b]				0.548#
Every week	18 (16.4)	8 (14.3)	10 (18.5)	
Every month	52 (47.3)	31 (55.4)	21 (38.9)	
Once every 3 months	26 (23.6)	11 (19.6)	15 (27.8)	
Less than every 3 months	12 (10.9)	5 (8.9)	7 (13.0)	
Never	2 (1.8)	1 (1.8)	1 (1.9)	

Characteristics at T1	Total (n=110) N (%)	Conventional schedule (n=56) N (%)	Experimental schedule (n=54) N (%)	*p*-value
Hospital costs (3 years)		n=43	n=42	
Follow-up visits		€56.387,89	€32.374,07	
Specialist		€51.431,10	€29.655,13	
NP		€2.538,10	€1.177,70	
Telephone consultation		€2.418,89	€1.541,24	
Diagnostics		€12.344,22	€6.931,95	
Laboratory testing		€322,76	€6,00	
Ultrasonography		€2.044,96	€819,96	
CT-scan		€775,89	€872,00	
FDG PET/CT scan		€2.771,42	€1.588,00	
Pathology/cytology		€6.429,19	€3.645,99	
Surgery		€2.450,00	€2.909,91	
Total costs		€71.182,11	€42.215,93	
Costs per patient over 3 years, mean±SD		€1655,40 ±921,3	€1005,14 ±745,05	**0.001**^

Data are expressed as n (%) unless otherwise specified
CSG Conventional Study Group; *ESG* Experimental Study Group; *AJCC* American Joint Committee on Cancer; *GP* general practitioner; *NP* nurse practitioner; *SD* standard deviation; *CT* computed tomography
[a]Highest level of education completed (high: vocational education, university; intermediate: secondary vocational education, high school; low: elementary school, low vocational education)
[b]Self-designed questions
[#]χ^2-test, [$]Independent student *t* test, *Fisher's Exact Test, [^]Mann-Whitney U test
Significant *p*-values in **bold**

differ between groups (p=0.466 and p=0.547 respectively)(Table 2). Adherence to assigned follow-up schedule and schedule satisfaction were not significantly related (Fisher Exact test, p=0.154). No significant difference was found between study groups in terms of melanoma-related GP visits (p=0.439) or when combining extra visits to the medical specialist with the melanoma-related GP visits (p=0.221). Of the 83 patients who paid extra GP visits, 46% did this only once (Table 2).
All patients reported to perform self-inspection, except one CSG and one ESG patient. Frequency of self-inspection did not differ significantly between groups (p=0.548)(Table 2).

Patient-reported outcome measures

Repeated measures ANOVA showed a significant between group effect on the IES (p=0.001) and the RAND-36 PCS (p=0.02). ESG patients had significantly lower IES mean scores at T1 and T3. ESG patients had a significantly lower RAND-36 PCS score at T1 (t-test: p=0.006) but not at T3 (t-test: p=0.264). Effect sizes were small. A significant decrease was found in mean scores over time on the CWS and IES, and an increase on the RAND-36 MCS and PCS scores (all p<0.001). Effect sizes were small. No significant interaction effects were found (Table 3).

Melanoma recurrences and deaths during the three year follow-up

At T3, 25 patients (13.9%) had been diagnosed with recurrent disease or a second primary, 15 CSG (16.1%) and 10 ESG patients (12%)(p=0.397). Cox proportional-hazards model showed no significant difference between groups in RFS (HR=0.71(0.32-1.58); p=0.400). Of the recurrences or second primaries, 15 were diagnosed within the first year[16] and 10 (40%) between T1-T3. No significant differences were found between groups in terms of locoregional and/or distant disease or second primaries (p=0.457) at T3. Sixteen recurrences (66,7%) were detected by the patients themselves and eight (33,3%) by the medical specialist: study groups did not differ in who detected a recurrence (p=0.204)(Table 4).
Of the 25 patients who developed a recurrence or second primary during the three years, 13 patients (7.2%) died of melanoma, six CSG and seven ESG patients (p=0.777). A Cox proportional-hazards model showed no significant difference between groups in DFS (HR=1.24(0.42-3.71); p=0.69).

TABLE 3 **Descriptives of patient-reported outcome measures at T1 and T3, and repeated measures analyses of variance (CSG: n=56, ESG: n=54)**

Questionnaire	Study group	T1 mean (SD)	T3 mean (SD)	Repeated measures ANOVA
STAI-S	Conventional	31.2 (8.3)	30.3 (9.4)	*F*=0.2; *p*=0.66 (group)
	Experimental	32.4 (8.1)	30.4 (7.9)	*F*=3.3; *p*=0.07 (time)
				F=0.5; *p*=0.48 (interaction)
CWS	Conventional	4.6 (1.5)	4.0 (1.8)	*F*=0.3; *p*=0.59 (group)
	Experimental	5.1 (2.2)	3.8 (1.0)	*F*=22.5; ***p<0.001*** (time), ES=0.18
				F=3.3; *p*=0.07 (interaction)
IES	Conventional	23.3 (14.4)	14.0 (17.0)	*F*=11.4; ***p=0.001*** (group), ES=0.12
	Experimental	14.0 (13.2)	6.2 (8.5)	*F*=31.5; ***p<0.001*** (time), ES=0.28
				F=0.23; *p*=0.64 (interaction)
RAND-36 MCS score	Conventional	49.6 (11.3)	53.5 (8.3)	*F*=0.004; *p*=0.95 (group)
	Experimental	48.6 (10.9)	54.3 (5.3)	*F*=21.2; ***p<0.001*** (time), ES=0.16
				F=0.81; *p*=0.37 (interaction)
RAND-36 PCS score	Conventional	48.9 (9.0)	52.4 (8.4)	*F*=5.4; ***p=0.02*** (group), ES=0.05
	Experimental	43.4 (11.3)	50.3 (10.6)	*F*=29.8; ***p<0.001*** (time), ES=0.22
				F=3.2; *p*=0.08 (interaction)

CSG Conventional Study Group; *ESG* Experimental Study Group
T1 at inclusion, shortly after diagnosis; *T3* three years later; *STAI-S* State-Trait Anxiety Inventory-State (range 20–80); *CWS* cancer worry scale (range 3–12); *IES* impact of event scale (range 15–75); *MCS* mental component summary of the RAND-36 (standardized mean 50, standard deviation of 10); *PCS* physical component summary of the RAND-36 (standardized mean 50, standard deviation of 10); *F* F-statistic; *ES* effect size; *SD* standard deviation; *ANOVA* analysis of variance
Significant *p*-values in **bold**

TABLE 4 **Descriptives of recurrences and deaths, and comparison between groups (CSG: n=93, ESG, n=87)**

Characteristics	Total (n=180) N (%)	Conventional schedule (n=93) N (%)	Experimental schedule (n=87) N (%)	*p*-value
Total recurrence or second primary during 3-year follow-up	25 (13.9)	15 (16.1)	10 (11.5)	0.397[#]
median time in days (range)	406 (179-1040)	369 (203-1040)	423 (179-984)	0.618[^]
Specifically				0.457*
Locoregional recurrence	11 (45.8)	8 (53.3)	3 (33.3)	
Distant recurrence	6 (25)	3 (20)	3 (33.3)	
Locoregional + distant recurrence	2 (8.8)	2 (13.3)		
Second primary	5 (20.8)	2 (13.3)	3 (33.3)	
Missing	1		1	
Detection of recurrence or second primary				0.204*
Patient	16 (66.7)	11 (78.6)	5 (50)	
Specialist/NP	8 (33.3)	3 (21.4)	5 (50)	
Missing	1	1		
Died of melanoma during 3-years follow-up	13 (7.2)	6 (6.5)	7 (8)	0.777[#]
Median time in days (range)	780 (406-1169)	997 (415-1169)	712 (406-1017)	0.317[^]
Died of other cause	3 (1.7)	2 (2.2)	1 (1.1)	

Data are expressed as n (%) unless otherwise specified
CSG Conventional Study Group; *ESG* Experimental Study Group; *NP* Nurse Practitioner
[#]χ^2-test, [^]Mann-Whitney U test, *Fisher's Exact Test

Cost analysis

Total amount spent during three-years follow-up was €71.182,11 for the 43 CSG and €42.215,93 for the 42 ESG patients. Mean amount spent per ESG patient was significantly lower than that per CSG patient (p=0.001)(Table 2). Total cost reduction was 39%. No significant differences were found in total costs between the two hospitals.

Discussion

The current study showed that, three years after diagnosis, patients assigned to the reduced stage-adjusted follow-up schedule (ESG) reported levels of anxiety, cancer worry, and mental health-related quality of life similar to those of patients assigned to the follow-up schedule as currently advised in the Dutch Melanoma guideline. Moreover, ESG patients reported significantly lower levels of SRS. Additionally, over the three years, recurrences and second primary melanomas were detected within a comparable time period in both groups, and the number of patients dying from melanoma and time until death were equal. Lastly, a reduced stage-adjusted follow-up schedule results in a 39% cost reduction in the ESG. These results support our hypotheses of no differences in PROMs, recurrences and deaths between study groups, and of lower costs in the experimental group. It suggests that a less frequent follow-up schedule than currently recommended in the Dutch Melanoma guideline does not negatively affect melanoma patients in terms of quality of life, nor the time until and the number of patients diagnosed with recurrent disease and/or dying from melanoma. Besides, costs would be decreased.

The present three-years results are in line with and thus support the one-year MELFO results.[16] As at one year, at three years, ESG patients even report to suffer less from SRS. The literature suggests that 50% of patients report having high anxiety before and during outpatient clinic visits.[26] Our findings suggest that a less frequent follow-up schedule, thus less exposure to such anxious events, is beneficial in the short- and longer-term because it induces fewer SRS. However, the effect size found of the between groups difference in SRS at three years is small, indicating that the difference is clinically not relevant, while the effect size at

one year was moderately large. This suggests that the difference in SRS between groups becomes clinically irrelevant over time.
As after one year[16], after three years, most ESG and CSG patients were satisfied with the assigned schedule. This implies that patients are content with the follow-up schedule suggested by their doctor, be it conventional or reduced. However, four-fifths of patients paid fewer or more melanoma-related visits, indicating that patients seek or decline medical attention when they judge it necessary or not.
A significantly higher percentage of the ESG than CSG patients paid extra visits to the medical specialist than scheduled. However, of those who paid extra visits, two-thirds of the ESG and more than half of the CSG patients paid only one extra visit during the three-years study period. Therefore it seems unlikely that extra visits will have affected the three-years results of the current study in terms of experienced quality of life or detection of a recurrence or second primary. Additionally, three-quarters of the patients paid extra visits to the GP, with again almost half (in both groups) paying only one extra visit in the three years of follow-up. The reason for these extra visits may be increased awareness of suspicious lesions, possibly resulting from effective education on self-inspection.[4,11-14,26-29]

The current three-year results show that the number of recurrences and second primary melanomas and the time until detection for patients with pathological sentinel node staged AJCC stage IB-IIC was independent of the assigned follow-up schedule, which is in line with the one-year MELFO results.[16] Almost two-thirds of the recurrences were detected within the first year after diagnosis and two-fifths between one and three years after diagnosis. This is conform literature, showing that the highest proportion of melanoma recurrences and second primaries is detected during the first year of follow-up and that the proportion declines over the following years.[4,9,13,14]
The present study shows that almost two-thirds of the patients detected a recurrence themselves, which is conform literature.[13,14,26] No differences were found between study groups, which suggests that patient information provided was comparable between study groups.
Overall, the three-year recurrence rate in the present study was 13.9%, which is comparable with recent literature reporting 14.7%.[4] It is slightly lower than the 19% reported in a retrospective study including AJCC stage IA-IIC melanoma patients and having a much longer follow-up time (range 0-26.6 years).[9] A first explanation for the higher percentage found in that study may be the inclusion of

patients who had not been sentinel-node staged, resulting in an underestimation of disease stage and consequently risk of recurrence.[30] Secondly, although most recurrences are detected within three years after diagnosis, some patients do develop a recurrence after three years.[9]

Thirteen patients in the current study died of their melanoma within three-years after diagnosis (7.2%), with no difference between follow-up schedule groups. This is slightly lower than the 8.2% reported in another prospective study. However, that study followed patients until four years after diagnosis.[4]

There is no consensus in the literature with respect to performing routine additional laboratory testing (biomarkers LDH, S-100B) and imaging (ultrasonography, chest X-ray, PET, MRI) during follow-up in pathological sentinel node staged AJCC IB-II melanoma patients, even in high risk melanoma patients (stage IIB/C), with some being in favor and others not.[31] The argument of those who are against is that three quarters of first recurrences are detected by patients themselves. They recommend to perform additional testing and imaging only when (distant) recurrent disease is suspected.[7,13,14,32] For patients with local, regional or metastatic disease, various treatment options are available, namely systemic treatment options like BRAF/MEK inhibitors, and immunologic strategies with CTLA4, PD-1-PD-L1 antagonists that result in significant improved survival rates.[33]

After three years, a less frequent follow-up schedule resulted in a considerable cost reduction (39%), as found after one year.[16] Healthcare costs are high, financially burdening healthcare systems and societies. The present study shows that a reduced stage-adjusted follow-up schedule is cost-effective, as well as safe for patients. Additionally, less frequent follow-up will save healthcare providers time, now and in the future, considering the increasing melanoma prevalence. Increasingly, in the Netherlands, melanoma trained nurse practitioners provide follow-up and specific patient melanoma (E-health) education in dedicated melanoma clinics.[29] This will further reduce costs in melanoma care.
The current study has some limitations. Firstly, 23% of the patients declined to participate at three years after diagnosis. However, this percentage is lower than the drop-out rate in another prospective study in melanoma patients[4]. Fortunately, no differences were found in baseline characteristics and PROMs between the patients who did and did not complete T3 questionnaires. Secondly, power

analysis showed that 89 patients per group were needed. We commenced with 93 in the CGS and 87 in the ESG. Due to drop-out over three years, the number of patients analyzed at T3 is lower than envisaged. However, no differences in socio-demographic and illness-related variables were found between the participants in the two study groups at T1[16], nor at T3. Thirdly, due to small sample size, some analyses performed should be interpreted carefully.

Conclusion

The three-years results of the MELFO study seem to support the notion that a reduced stage-adjusted follow-up schedule is an appropriate, safe, and cost-effective alternative for pathological, sentinel node staged, AJCC stage IB-IIC melanoma patients in terms of quality of life, recurrences, deaths, and financial costs to the follow-up regime as advised in the current melanoma guideline.

Acknowledgments

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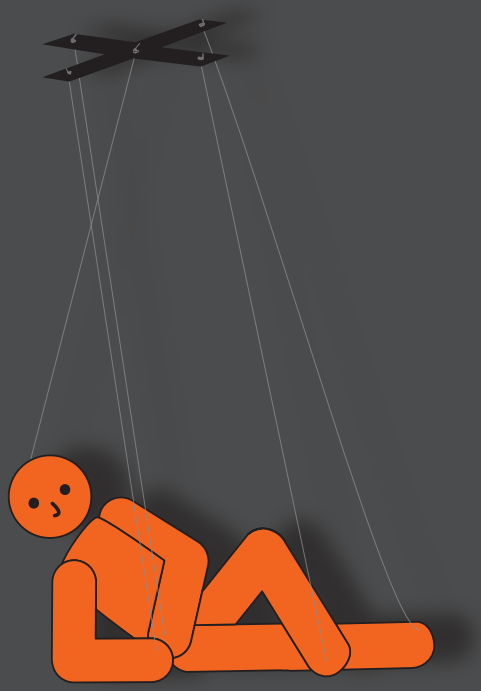
2B

ASO author reflections: stage-adjusted reduced follow-up of melanoma patients is justified and cost effective, until biomarkers to predict prognosis have been identified



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Past

The incredible rise in melanoma health care costs urgently demands a reduction in these costs where appro- priate.[1] Nevertheless, cancer patients demand frequent and close follow-up out of fear of recurrence. Historically, melanoma patients have been followed regularly, with limited therapeutic options in case of disease progression.[2] In addition, survival benefit as a result of follow-up has never been demonstrated.[3] There is a lack of international consensus regarding the follow-up frequency of melanoma patients,[4] and evidence regarding the optimal follow-up frequency of these patients with respect to disease-free and overall survival, patients' quality of life (QoL), and costs is highly needed.

Present

The current randomized controlled MELFO study compared two groups of stage IB–IIC melanoma patients, 3 years after diagnosis.[5] The first group received follow-up as advised in the guideline, while the second group received a stage-adjusted, less frequent follow-up schedule. Patients' QoL, anxiety, satisfaction regarding follow-up, and disease-free and overall survival were comparable, but a 39% cost reduction was found in those who were less frequently followed-up. A reduced and stage-adjusted follow-up schedule could be a step forward in better distribution of resources, such as finances, time, and manpower.

Future

Several questions need to be answered in the future to determine the optimal, safe, (cost)-effective follow-up that will benefit all melanoma patients.[3] Apart from recurrence detection, mental support and patient education are important after-care goals for melanoma patients with any stage of disease.[6,7] Now that several effective therapeutic adjuvant systemic treatment options with drug targeting and/or immunotherapy have become available, follow-up has become even more complex.[8] What is the best strategy to improve OS in stage IB–II melanoma? Adjuvant therapy of high-risk stage II patients or treatment at the time of recurrence? How to select patients who will benefit from adjuvant treatment while sparing those who are unlikely to benefit from toxic effects? If melanoma biomarkers could be identified that can better predict the potential to metastasize than the current prognostic factors do, a personalized follow-up, including emotional support and patient education, could be delivered even more (cost) effectively. Currently, stage-adjusted follow-up is the best personalized follow-up approach for stage IB–II melanoma.

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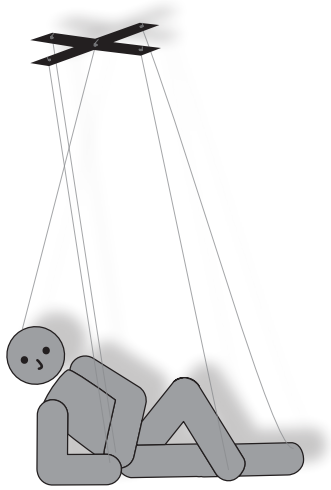
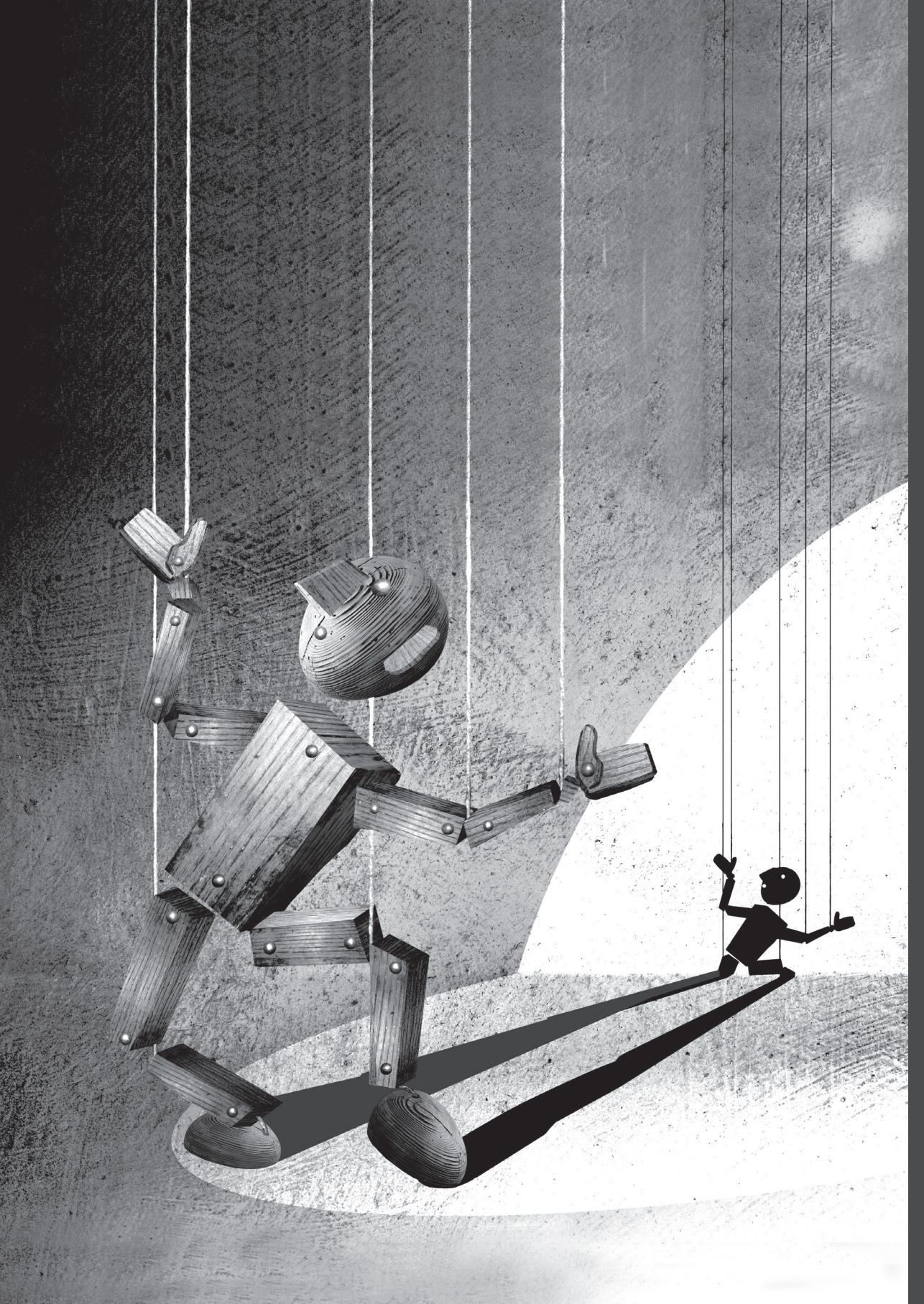
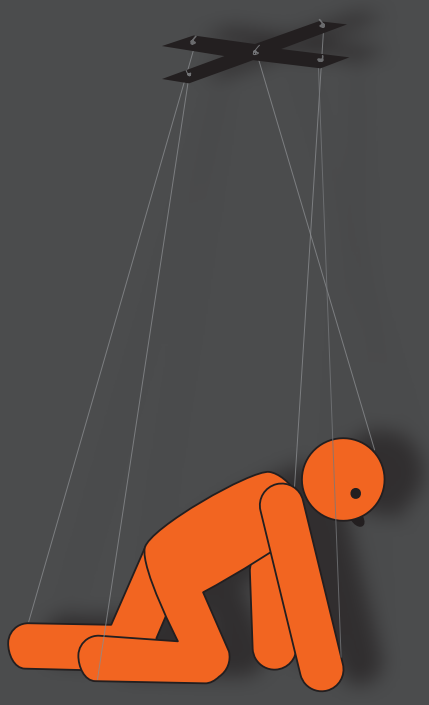




3

Increase of sentinel lymph node melanoma staging in the Netherlands; still room and need for further improvement



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Melanoma Management 2020

Abstract

Aim
To investigate implementation of the 7th AJCC melanoma staging with sentinel lymph node biopsy (SLNB) and associations with socioeconomic status (SES).

Patients & Methods
Data from the Netherlands Cancer Registry on patient and tumor characteristics were analyzed for all stage IB-II melanoma cases diagnosed 2010–2016, along with SES data from the Netherlands Institute for Social Research.

Results
The proportion of SLNB-staged patients increased from 40% to 65% ($p<0.001$). Multivariate analysis showed that being female, elderly, or having head-and-neck disease reduced the likelihood of SLNB staging.

Conclusions
SLNB staging increased by 25% during the study period but lagged among elderly patients and those with head-and-neck melanoma. In the Netherlands, SES no longer affects SLNB staging performance.

Introduction

Sentinel lymph node biopsy (SLNB) in patients with American Joint Committee on Cancer (AJCC) stage IB-II melanoma was introduced in the Netherlands in 1996. The Dutch Society of Surgical Oncology and several regional working groups of the Netherlands Comprehensive Cancer Organization disseminated the SLNB staging model in the Netherlands.

Prospective studies, such as the Multicenter Selective Lymphadenectomy Trial (MSLT)-I and the more recent MSLT-II, demonstrated the staging and prognostic value of SLNB for stage IB-II melanoma.[1-4] Most patients are pleased with the outcomes of this minimally invasive staging procedure that yields good information with limited negative effects on quality of life.[5,6] MSLT-I results showed that SLNB is a low-morbidity procedure for staging the regional nodal basin in early melanoma and that complete lymph node dissection (CLND) is associated with lower morbidity compared to therapeutic lymph node dissection.[2-4,7] MSLT-II indicated an association of CLND with increased regional disease control. However, this benefit did not involve increased melanoma-specific survival compared to patients managed with positive SLNB and regular ultrasonography of the lymph node basin, with therapeutic lymph node dissection in case of regional recurrence.[4]

Interferon (IFN) has been extensively studied in different regimens (high, intermediate, low dose, pegylated IFN, with or without induction phase, shorter and longer maintenance dose) in 15 adjuvant trials for advanced melanoma, but with a minimal effect overall.[8] The prognosis of stage III and IV melanoma has improved considerably in the last 10–15 years through targeted therapy with BRAF inhibitors (dabrafenib and vemurafenib) in BRAF-mutated disease, or with MEK inhibitors (trametinib and cobimetinib) and immunotherapy with the immune checkpoint inhibitors anti CTLA-4 antibody (ipilimumab) and anti-PD1 antibodies (nivolumab and pembrolizumab).[9] In addition to these new, effective systemic therapies, two new intralesional therapies are in current trials. One is intralesional local melanoma treatment with talimogene laherparepvec, an oncolytic virus therapy. The other involves chemoablation with intralesional Rose Bengal, a small molecule oncolytic immunotherapy.[10,11] Either of them, used for the treatment of in-transit metastases or metastatic disease, may also enhance the patient immune system. Targeted

and/or immunotherapy treatment may improve disease-free and overall survival for patients with stage III and IV melanoma. Optimal staging of clinical stage IB-II melanoma is therefore indicated to identify patients with high-risk stage IIIA disease who might also benefit from these new therapies.

Seventeen years after the introduction of SLNB staging for melanoma, this procedure was performed in less than 50% of all eligible patients in the Netherlands. Considerable practice variation has been observed in SLNB procedures among the eight cancer regions of the Comprehensive Cancer Organization, ranging from 22.5% to 56.5%.[12,13] The revised Dutch melanoma guideline of 2012 advised SLNB staging for stage IB-II melanoma. However, in 2014, only 25% of melanoma-treating specialists in the Netherlands endorsed the need for SLNB for regional staging of stage IB-II disease. Residents endorsed at a higher rate, but still at only 44%.[14] Furthermore, in patients with head-and-neck melanoma, older patients, and patients with a low social economic status (SES), SLNB was less frequently performed. It was used more often in patients with T3 melanomas and those diagnosed with melanoma in a university hospital.[12,13,15]

The aim of the current study was to update information about the performance of SLNB in the Netherlands in clinical stage IB-II melanoma after implementation of the 7th edition of the AJCC staging manual in 2010[16], which included sentinel lymph node staging. This aim was selected because high-risk patients might benefit from new systemic therapies and to allow comparison of these results with previous reports from the Netherlands among cancer regions and provinces and investigation of the role of SES in SLNB implementation.

Methods

Study population

This study included all patients with localized melanoma stage IB-II diagnosed 2010–2016. Data were retrieved from the Netherlands Cancer Registry, embedded within the Netherlands Comprehensive Cancer Organization.[17] This population-based registry relies on notification by the automated nationwide network and registry of histopathology and cytopathology in the Netherlands and is complemented by other sources such as a national registry of hospital discharge and

radiotherapy institutes. Data collection was conducted according to the declaration of Helsinki ethical principles for medical research involving human subjects.[18] After notification, fully trained registrars routinely collected data from pathology reports and patient files in all Dutch hospitals. Data were collected on patient and tumor characteristics, such as age, sex, tumor localization of the primary melanoma, and tumor stage.
Information about the performance and outcome of SLNB was retrieved from the medical records. Patients with clinically suspicious or palpable lymph nodes, distant metastases, and/or a history of lymph node dissection were excluded.
SES scores were assigned to different postal code areas by the Netherlands Institute for Social Research and calculated based on income, employment, and level of education.[19] Calculated scores give an estimate of the SES in the particular postal code area where a patient resides. Calculated SES scores are divided into five groups: SES=1 (low) to SES=5 (high).

To render the data from this study comparable to those from previous studies with respect to the SLNB staging in the Netherlands, the Northeastern part of the country was compared to the rest of the Netherlands, as were the eight cancer regions and provinces.[12,13] This approach made it possible to investigate the role of the Dutch Society of Surgical Oncology and several regional working groups of the Netherlands Comprehensive Cancer Organization in the dissemination of the SLNB approach.

Statistical analysis

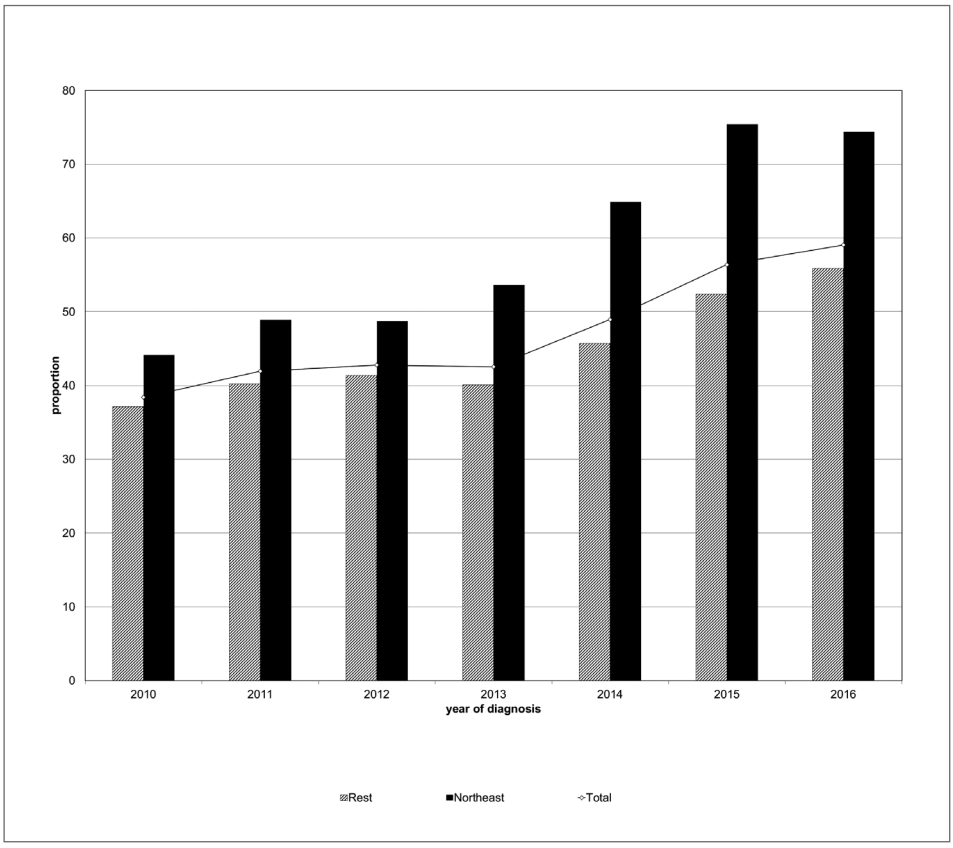
Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). Patient characteristics were compared between the Northeastern provinces and the rest of the Netherlands using Chi-square or Mann–Whitney U tests (the latter with nonnormally distributed data). Also, patient characteristics from SLNB-positive and -negative cases were compared. Multivariable logistic regression analysis was performed to estimate the odds for undergoing SLNB. Values were adjusted for factors that could influence the decision to perform SLNB (e.g., region, age, primary lesion location, Breslow thickness, pathological stage of primary tumor, SES). $P<0.05$ was considered statistically significant.

Results

During the study, a total of 19,100 patients with stage IB-II melanoma were registered (9344 males (49%) and 9756 females (51%)). SLNB was performed in 9163 (48%) overall. The proportion of melanoma patients who received SLNB increased, however, from 40% in 2010 to 65% in 2016 (Figure 1). The procedure was performed significantly more often in the Northeastern part of the Netherlands compared to the rest of the country ($p<0.01$; Table 1 and Figure 1). An overview of the percentage SLNBs performed in each province in the Netherlands is presented in Figure 2.
Of the 9163 patients who underwent SLNB, positive nodes were found in 1877 patients (20%) (Table 2). No differences were found in patient or tumor characteristics and sentinel node positivity between the Northeastern part of the Netherlands and the rest of the country (data not shown).

Median age at diagnosis in the SLNB group was 58 (interquartile range (IQR), 47–68) years, compared to 67 (IQR, 53–78) years in the group that did not undergo SLNB ($p<0.001$). Tumors in the SLNB group were thicker (median Breslow thickness, 1.7 (1.2–2.8) mm, compared to 1.3 (0.9–2.7) mm in the non-SLNB group ($p<0.01$)), and tumor stage at diagnosis was significantly higher ($p<0.01$). Most primary melanomas were located on the trunk (37%), followed by the lower limb (27%), upper limb (21%), and head-and-neck region (15%). Significantly fewer SLNBs were performed among patients with melanomas located in the head-and-neck area ($p<0.01$; Table 1). Figure 2 presents an overview by province of the percentage of SLNBs performed in melanomas located in the head-and-neck region, trunk, and limbs. No significant differences in SES were found between the SLNB and non-SLNB groups ($p<0.2$; Table 1).
After adjustment for sex, age, tumor location, Breslow thickness, SES, and tumor stage, multivariate analysis showed that SLNBs were more often performed in the Northeastern part of the Netherlands (odds ratio (OR), 2.2; 95% confidence interval (CI), 2.01–2.41; Table 3). Females were less likely to undergo SLNB (OR, 0.9; 95% CI, 0.84–0.96)($p<0.05$), and SLNB rates decreased with increasing age. Patients with head-and-neck melanomas underwent SLNBs less often (head/neck vs. limb: OR, 0.24; 95% CI, 0.21–0.27)($p<0.05$). SLNB was performed slightly more often among patients from a high SES class (score<5) when compared to low SES (OR, 1.2; 95% CI, 1.04–1.29)($p<0.05$; Table 3).

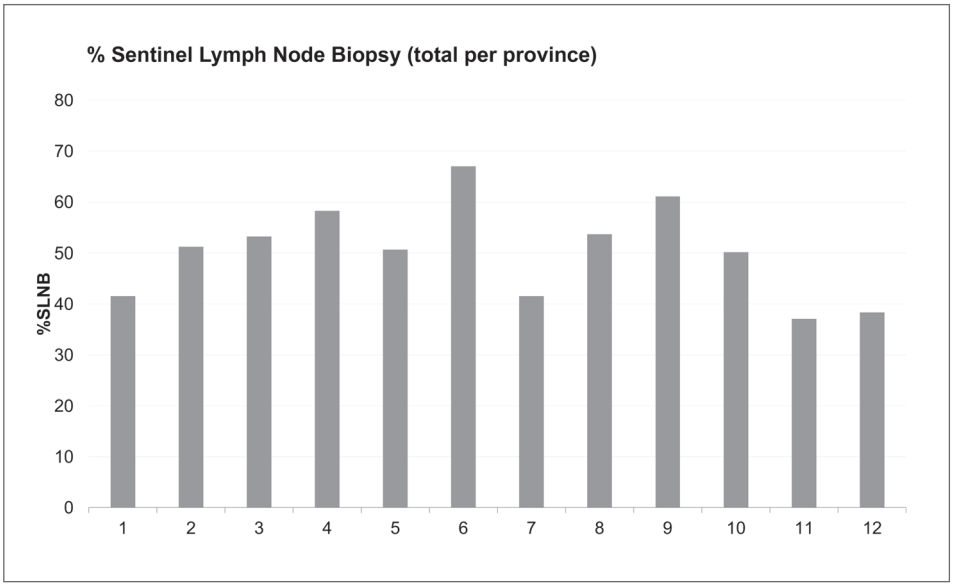
FIGURE 1 **Trend in the proportion of SLNBs performed per year of diagnosis in all patients with IB-II melanoma in the Netherlands; comparison among topographical regions**

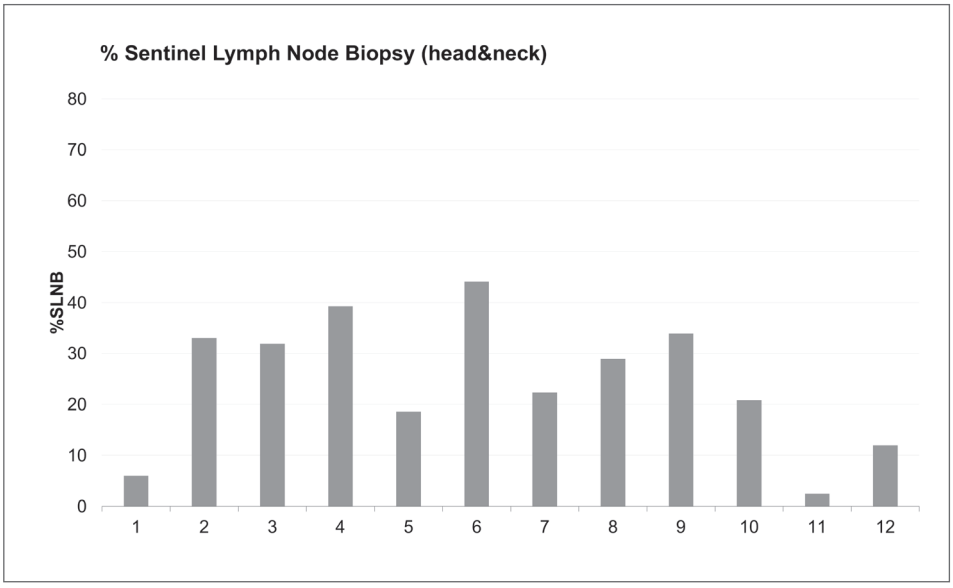


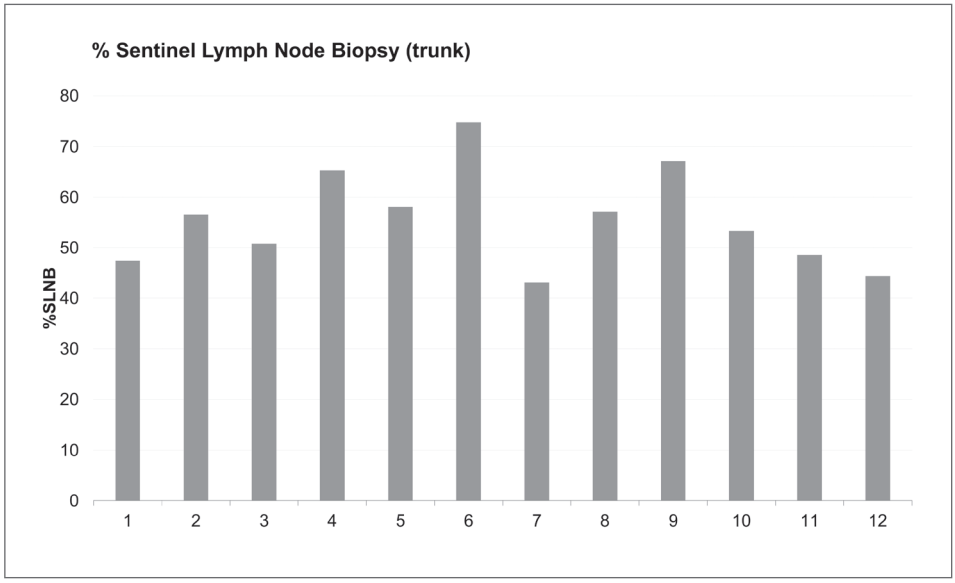
Number of patients by region

Rest	**1747**	**1822**	**1978**	**2505**	**2504**	**2470**	**2644**
Northeast	**376**	**450**	**474**	**552**	**510**	**517**	**551**
Total	**2123**	**2272**	**2452**	**3057**	**3014**	**2987**	**3195**

FIGURE 2 **Percentages of sentinel lymph node biopsies per province in the Netherlands; comparison among different anatomical locations of the primary melanoma**






% Sentinel Lymph Node Biopsy (trunk)
%SLNB
0
10
20
30
40
50
60
70
80
1
2
3
4
5
6
7
8
9
10
11
12

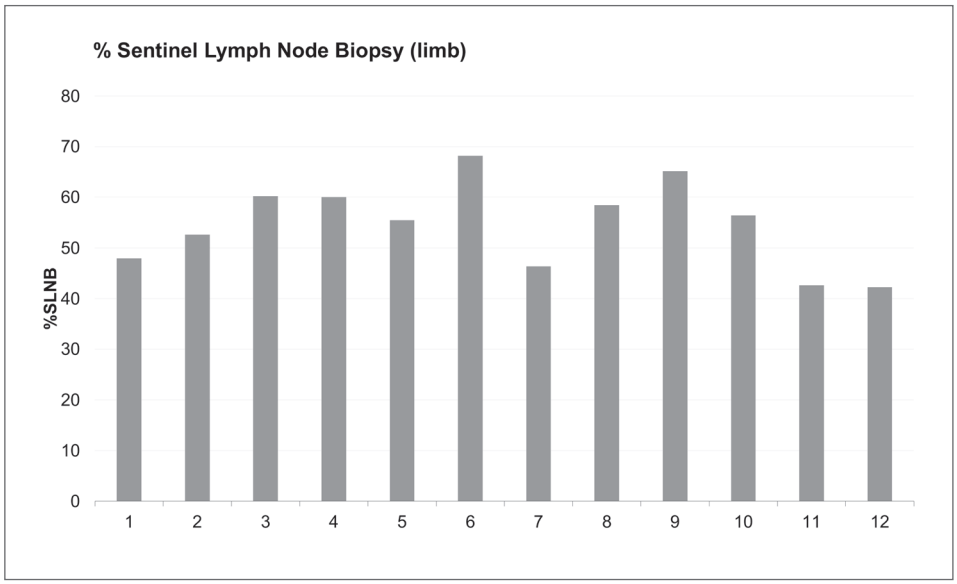

% Sentinel Lymph Node Biopsy (limb)
%SLNB
0
10
20
30
40
50
60
70
80
1
2
3
4
5
6
7
8
9
10
11
12

TABLE 1 **Characteristics of all patients with stage IB-II melanoma in the Netherlands, diagnosed 2010-2016, comparison between groups (sentinel lymph node biopsy (yes/no))**

	SLNB performed		No SLNB performed		Total		
	n	%	n	%	n	%	*p*-value
Gender							0.3*
Male	4518	49	4826	49	9344	49	
Female	4645	51	5111	51	9756	51	
Age (years) at diagnosis							**<0.01***
15-29	392	4	229	2	621	3	
30-44	1489	16	1001	10	2490	13	
45-59	3120	34	2258	23	5378	28	
60-74	3278	36	3254	33	6532	34	
>75	884	10	3195	32	4079	21	
Median age (years) (Q_1-Q_3)	58	(47-68)	67	(53-78)	62	(49-73)	**<0.01#**
Location primary							**<0.01***
Head/neck	590	6	2269	23	2859	15	
Trunk	3737	41	3296	33	7033	37	
Arm	2017	22	2048	21	4065	21	
Leg	2814	31	2308	23	5122	27	
Overlapping	5	0	16	0	21	0	
Breslow Thickness (mm)							**<0.01***
<1	1155	13	3307	33	4462	23	
1-2	4352	47	2983	30	7335	38	
2-3	1710	19	1136	11	2846	15	
3-4	808	9	635	6	1443	8	
>4	1020	11	1421	14	2441	13	
Unknown	118	1	455	5	573	3	
Median Breslow Thickness (Q_1-Q_3)	1.7	(1.2-2.8)	1.3	(0.9-2.7)	1,5	(1.1-2.75)	**<0.01#**

	SLNB performed		No SLNB performed		Total		
	n	%	n	%	n	%	*p*-value
pT							**<0.01***
1B	1132	12	3254	33	4386	23	
2	4503	49	3099	31	7602	40	
3	2539	28	1764	18	4303	23	
4	952	10	1372	14	2324	12	
X	37	0	448	5	485	3	
SES							0.2*
1 (Low)	1560	17	1712	17	3272	17	
2	1729	19	1843	19	3572	19	
3	1877	20	2100	21	3977	21	
4	1876	20	2109	21	3985	21	
5 (High)	2121	23	2173	22	4294	22	
Region[a]							**<0.01***
North-Eastern part[b]	2044	22	1386	14	3430	18	
Rest[c]	7119	78	8551	86	15670	82	
Total	9163	48	9937	52	19100	100	

Data are displayed as n (%) or median (interquartile range)
SLNB Sentinel Lymph Node Biopsy; *Q1-Q3* interquartile range; *pT* pathological primary tumor stage; *SES* Social Economic Status
[a]Topographic region in the Netherlands, [b]North-Eastern part (Groningen, Friesland, Drenthe and Overijssel) and [c]Rest of the provinces in the Netherlands
*χ^2-test, #Mann-Whitney U test
Significant *p*-values in **bold** ($p<0.05$)

TABLE 2 **SLNB positivity in Dutch patients with melanoma between 2010 and 2016, by topographical region in the Netherlands (n=9163)**

	North-Eastern part[a]		Rest[b]		Total		
	n	%	n	%	n	%	*p*-value
SLNB							0.7*
Negative	1595	78	5598	79	7193	79	
Positive	425	21	1452	20	1877	20	
Not found/unknown	24	1	69	1	93	1	
	2044	22	7119	78	9163	100	

Data are displayed as n (%)
SLNB Sentinel Lymph Node Biopsy
[a]North-Eastern part (Groningen, Friesland, Drenthe and Overijssel) and [b]Rest of the provinces in the Netherlands
* $\chi 2$-test

Discussion

This study showed that in 2016, a quarter of a century after its introduction, SLNB was performed in only 65% of eligible Dutch patients with melanoma. In females, elderly patients, and those with head-and-neck melanoma, the staging procedure was performed even less frequently. However, SES no longer significantly affected the likelihood of SLNB staging, a change from the association before 2010.[12]

The 4th revision of the Dutch melanoma guideline published in 2004 advised using SLNB in patients with stage IB or higher melanoma who wanted to be optimally informed about their prognosis. The SLNB staging procedure was therefore not part of the standard workup of patients with clinical stage IA-II melanoma. Since 2004, the percentage of SLNBs performed in cases of melanoma increased in the Netherlands from 24% to 55% in 2011.[12,13]
The 5th revision of the Dutch melanoma guideline in 2012, based on the 7th edition of the AJCC staging manual that went into effect in 2010[16], advised SLNB for stage IB-II melanoma and discussed the potential benefits and drawbacks of CLND in case of sentinel node positivity. Recently, effective adjuvant targeted and immune

TABLE 3 **The likelihood of performing SLNB adjusted for multiple variables in Dutch patients with melanoma: a multivariate analysis**

		OR	95% CI	
Region	Northern part[a]	**2.20**	2.01	2.41
	Rest[b]	ref		
Gender	Male	ref		
	Female	**0.90**	0.84	0.96
Age (years) at diagnosis	15-29	ref		
	30-44	**0.79**	0.64	0.97
	45-59	**0.67**	0.55	0.82
	60-74	**0.45**	0.37	0.54
	>75	**0.11**	0.09	0.13
Location primary	Head/neck	**0.24**	0.21	0.27
	Trunk	**0.90**	0.80	1.03
	Limb[c]	ref		
	Overlapping	**0.26**	0.09	0.70
Breslow Thickness (mm)	<1	ref		
	1-2	**2.20**	1.70	2.90
	2-3	**2.30**	1.60	3.30
	3-4	**2.10**	1.50	3.10
	>4	**2.00**	1.40	2.80
	onbekend	**2.60**	1.80	3.90
pT	1B	ref		
	2	**2.60**	2.00	3.30
	3	**3.60**	2.50	5.10
	4	**2.20**	1.60	3.20
	x	**0.20**	0.12	0.33
SES	1 (Low)	ref		
	2	1.02	0.91	1.14
	3	1.06	0.95	1.18
	4	1.05	0.94	1.17
	5 (High)	**1.17**	1.04	1.29

Data are displayed as Odds Ratio (OR) with 95% Confindence Interval (CI)
Ref Reference; *pT* pathological tumor stage; *SES* Social Economic Status
[a]North-Eastern part (Groningen, Friesland, Drenthe and Overijssel) and [b]Rest of the provinces in the Netherlands, [c]Limb (lower and upper extremity)
Significant Odds Ratios in **bold** ($p<0.05$)

systemic therapies for stage III melanoma have become available. Therefore, adequate staging is even more important, emphasizing the need for insight into the current application of SLNB in the Netherlands.

Large regional differences persist in the use of SLNB in stage IB-II melanoma. Melanoma guidelines are more often met in academic centers.[20] In the Northeast, the percentage was in 74% in 2016, compared to 56% in the rest of the Netherlands ($p<0.01$). These results are promising and in keeping with the trend in the Northeast, but higher percentages of SLNB performance should be feasible. The current 65% rate of SLNBs is comparable to previously reported percentages in the United States, from 47% to 60%.[21-24] However, the percentage of SLNB performed in melanoma remains lower than the almost 80% rate in breast cancer.[25] An explanation might be that in melanoma, physicians who perform the diagnostic excision and re-excision (if indicated) lack the surgical skills or opportunity to perform SLNB. Another reason might be that physicians found no indication for SLNB based on MSLT-II results, because it is only a diagnostic procedure and no longer a therapeutic intervention.

SLNB also can be applied without a good basis. A recent Dutch study showed that use of SLNB in non-eligible melanomas according to the Dutch melanoma guidelines was 2.9%.[26] In Germany, the percentage of SLNB staging for melanoma is 88%.[27,28] An explanation for the high percentage might be that German dermatologists are 'melanomologists' who manage the whole melanoma surgical and systemic treatment in-house.[29] In contrast, in the Netherlands and the United States, the melanoma health care landscape is more fragmented, divided among surgeons, dermatologists, plastic surgeons, head-and-neck surgeons, medical oncologists, and in the Netherlands, even per province and cancer region. This mosaic of care might explain the great variation in SLNB uptake not only in the Netherlands but also in countries like the United States.
Age and melanoma located in the head-and-neck region remain important predictors of whether to perform SLNB. As in this study, an investigation in the general U.S. population found noncompliance with National Comprehensive Cancer Network melanoma guidelines on SLNB for elderly patients and for melanoma located in the head and neck.[20,24,30] With melanoma, as for breast cancer, comorbidity could be a limiting factor in whether or not to perform SLNB. It is also possible that elderly patients, their family, caregivers, and treating physicians decide on a more conservative treatment approach balanced against an existing shorter life expectancy.

Performance of SLNB in women was less likely in the Netherlands, although median Breslow thickness was 1.40 (IQR, 1.0–2.5) mm in women compared to 1.70 (IQR, 1.1–3.0) mm in men. This finding of lower rates of SLNB in women is remarkable because it was adjusted for other factors (e.g., age, primary lesion location, pathological stage of the primary tumor, Breslow thickness, SES) that could influence the decision to perform SLNB. Recently, El Sharouni et al. hypothesized two explanations for the differences in sex-specific decision-making: medical information may be perceived differently, or there may be a clinician-specific sex bias when approaching and informing female patients.[26]

The SLNB positivity rate in this study was 20%, which is comparable to other studies showing between 15% and 22%,[28,31,32] as was the location of the primary melanoma.[28] We found that SLNB was performed in 21% of eligible patients with head-and-neck melanoma in the Netherlands, compared with 17% in a study that included data up to 2014.[26] Noncompliance with SLNB recommendations was also found in the U.S. general population for head-and-neck primary lesions (OR, 2.0; 95% CI, 1.9–2.2).[20,24] SLNB procedures in the head-and-neck area are technically difficult, even for experienced surgeons, because of the small incisions, critical anatomical structures, and great variation in atypical and/or multiple drainage sites.[33-36]. SLNBs and re-excision procedures of limb and trunk melanoma can be safely performed under local anesthesia.[37] In contrast, SLNBs for melanoma located in the head-and-neck region often require general anesthesia that might introduce additional morbidity. These two reasons might explain the low rates of SLNB performed in patients with head-and-neck melanoma.
In contrast to a previous study performed in the Netherlands, our findings demonstrate that SES no longer affected SLNB rates during the time period studied.[15] Although SLNB was performed slightly more often among patients with high SES, it is now routinely performed in the Netherlands for patients with lower SES, as is the case in Germany, where Livingstone et al. also found no SES influence on SLNB rates.[28]

SLNB for melanoma is a minimally invasive staging procedure, accompanied by minimal treatment–related short- and long-term morbidity.[5,7,38-41] Negative SLNB had no negative effects on quality of life.[6] The quality of life in Dutch melanoma survivors after axillary or inguinal SLNB, with or without CLND, is even better than that in a norm group.[5] This suggests that performing SLNB in melanoma patients is

a minimal invasive procedure beneficial for the patients without affecting quality of life. Compliance with national melanoma guidelines and using an integrated multidisciplinary approach through case discussions in the melanoma tumor board will improve melanoma-specific, disease-free, and overall survival. In addition, there must be room for shared decision making among treating patients, physicians, and caregivers, with specific assessments of each patient's ultimate goals of care.

The new, successful treatment of advanced melanoma with targeted and immunotherapies has changed overall melanoma care in the Netherlands. Each case of advanced melanoma today is discussed at one of 13 melanoma centers in the Netherlands with respect to (combined) treatment. The promising results achieved with the targeted and immunotherapies have meanwhile led to increased consultations between hospitals and melanoma centers with regard to treatment of patients with sentinel node–positive melanoma. The expectation is that further implementation of SLNB staging will now rapidly take place in the Netherlands.

Limitations

There are several limitations with this study. The reason for offering the patient SLNB or not as a minimally invasive staging procedure of the regional nodal basin was unknown. Surgeons, plastic surgeons, head–neck surgeons, and dermatologists likely differed in reasons for staging a localized melanoma with SLNB, and the patient's reasons for accepting or declining a SLNB were not recorded. Also unknown was if the cases were discussed in a melanoma tumor board or if there was a consultation with the regional melanoma tumor board of one of the eight comprehensive cancer centers. Because of general data protection regulations in the Netherlands, the Comprehensive Cancer Center was unable to retrieve some percentage of SLNBs performed at the various hospitals, and instead data with respect to the provinces were provided.

Future perspectives

In addition to the importance of adequate staging in an era of novel therapies, other advantages should also be considered. First of all, follow-up after a negative SLNB can be reduced, along with the costs of melanoma follow-up in 39% of patients, without affecting quality of life.[41,42] Second, a personalized approach will be possible for sentinel lymph node–positive patients, using a wait-and-see policy and less frequent CLND.[9,43,44]

In the optimization of sentinel lymph node staging in a non-invasive manner, ultrasonography is not an effective substitute for SLNB.[45] However, a promising technology of targeted fluorescence imaging in clinical stage IA-II melanoma is currently being explored using multispectral optoacoustic tomography (MSOT).[46] MSOT provides both anatomical and biological information and has the potential to identify sentinel lymph node metastatic involvement in patients with melanoma. Thus, when surgery is indicated, removal of only 'positive' sentinel lymph node(s) for further pathology examination and mutation analysis is possible.

Two recent studies, DeCOG and MSLT-II, showed that overall survival after a positive SLNB and CLND was not different from a delayed therapeutic lymph node dissection in case of a regional recurrence.[4,47] Will both of these negative studies now lead to less frequent offering of SLNB for stage IB-II melanoma according to the current 8th edition of the AJCC staging? Is SLNB, a minimally invasive staging procedure that provides optimal staging information with no clear survival benefit, still indicated? With the advent of effective systemic treatments for melanoma, including targeted or immunotherapies, optimal staging of stage IB-II melanoma appears to be a sine qua non. In the case of a positive SLNB, a melanoma tumor board should discuss further treatment decisions based on information about the number of positive SLNBs, nodal basin site, and SLNB tumor burden (measured by maximum diameter of the largest focus or percentage area of the node). Further studies have to be performed to see if adjuvant systemic treatment for stage IIIA melanoma will improve disease-free and/or overall survival.

Conclusion

Twenty-three years after the introduction of minimally invasive sentinel lymph node staging for melanoma, SLNB was performed in 65% of the eligible Dutch melanoma patients in 2016, although less often in elderly patients, females, and those with head-and-neck melanoma. Age and tumor location in the head-and-neck region might no longer be exclusion criteria, leaving only severe co-morbidity or short life expectancy as contraindications. In the Netherlands, SES has ceased to be associated with the use of SLNB staging. Until promising non-invasive procedures emerge in the field of melanoma staging, further implementation of SLNB and adherence to melanoma guidelines, in accordance with the current 8th AJCC staging in melanoma, are indicated, especially in view of the increasingly available effective drug targeted and/or immune-therapy for high-risk melanoma.

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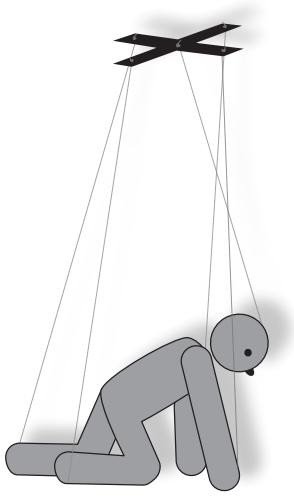

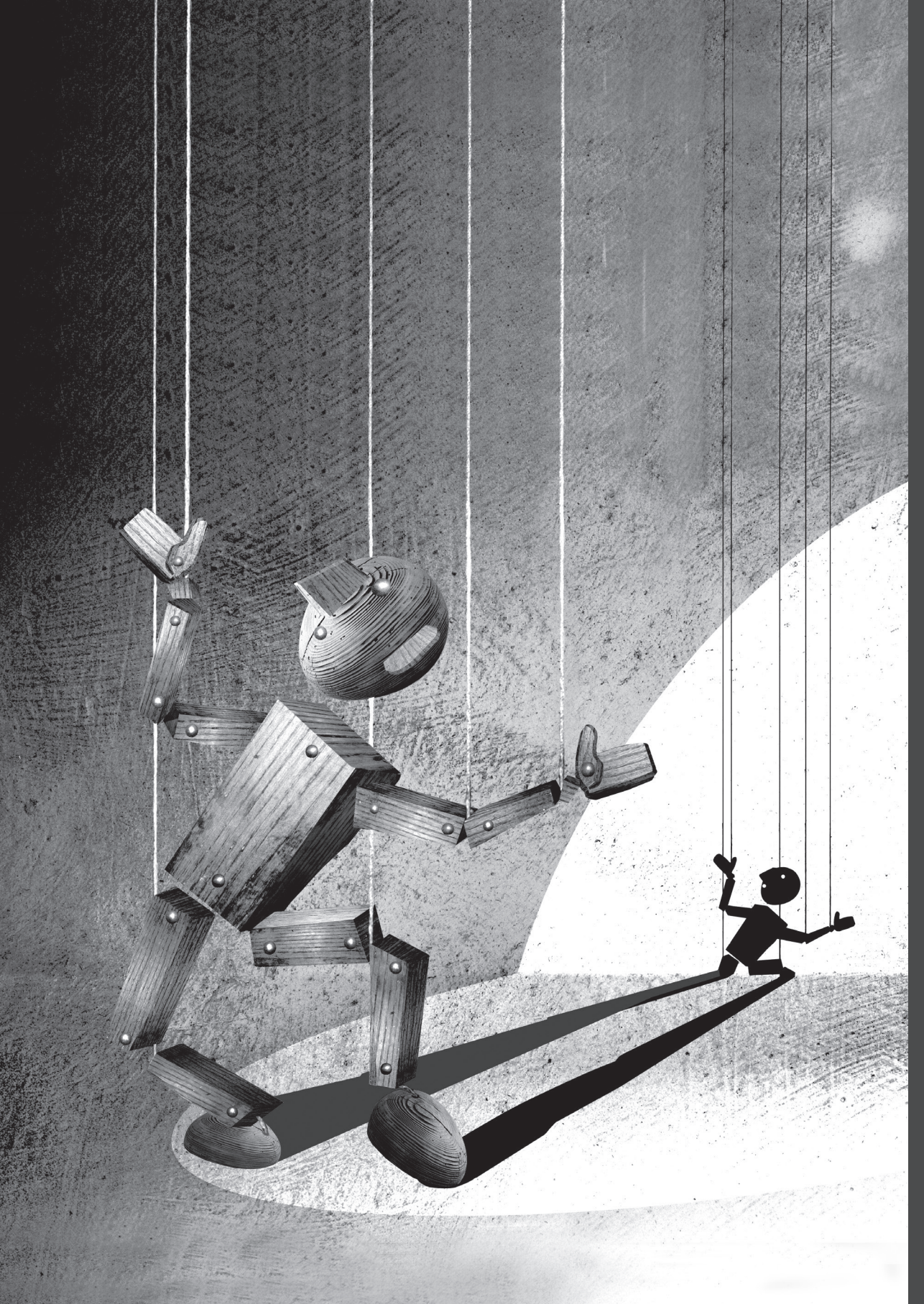

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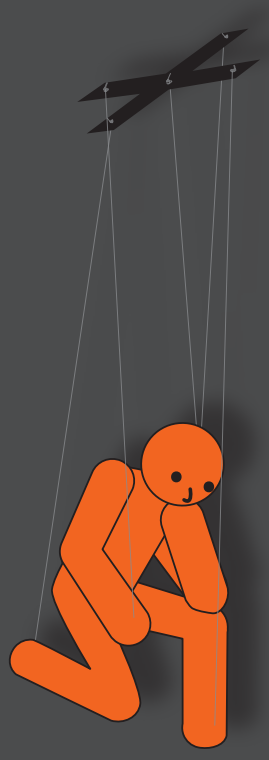
Obesity is not associated with decreased recurrence-free period, melanoma-specific survival, and overall survival in clinical stage IB-II melanoma patients



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Abstract

Introduction
Clinicopathologic characteristics are of prognostic value in clinical stage IB-II melanoma patients. Little is known about the prognostic value of patient-related characteristics. Obesity has been associated with an increased risk for several cancer types and worsened prognosis after cancer diagnosis. This study aims to examine effects of obesity on outcome in clinical stage IB-II melanoma patients, next to the effects of clinicopathologic and patient-related characteristics.

Methods
Prospectively recorded data of clinical stage IB-II melanoma patients who underwent SLNB between 1995-2018 at the UMCG were collected from medical files and retrospectively analyzed. Cox regression analyses were used to determine associations between tumor and patient-related variables and recurrence-free period (RFP), melanoma-specific survival (MSS), and overall survival (OS). Variables included were: obesity (BMI>30), location, histology, Breslow thickness, ulceration, mitotic rate, SLNB status, gender, age, and social-economic-status (SES).

Results
Of the 715 patients included, 355 (49.7%) were women, median age was 55 (range 18.6-89) years, 149 (20.8%) were obese. Obesity did not significantly affect RFP (adjusted HR=1.37;95%CI=0.96-1.96;p=0.08), MSS (adjusted HR=1.48;95%CI=0.97-2.25;p=0.07), and OS (adjusted HR=1.25;95%CI=0.85-1.85;p=0.25). Increased age, arm location, increased Breslow thickness, ulceration, increased mitotic rate, and positive SLNB status were significantly associated with decreased RFP, MSS and OS. Histology, sex and SES were not associated.

Conclusions
Obesity was not associated with recurrence-free period, melanoma-specific or overall survival in clinical stage IB-II melanoma patients.

Introduction

The increasing incidence of melanoma is mainly attributed to the depleting ozone layer that increased the intensity of ultraviolet radiation and to lifestyles changes, such as sun-seeking behavior and the use of tanning beds.[1,2] At the same time there are changes in the distribution and stage of melanoma at diagnosis. There are more melanomas being diagnosed with a higher percentage of thin melanomas, resulting in an increase of the prevalence of melanoma.[3]

The prognosis of clinical stage IB-II melanoma patients is based on, and well-defined for, several tumor and clinicopathologic factors such as primary tumor site, Breslow thickness, mitotic rate, ulceration, regression, histopathologic subtype of melanoma, sentinel lymph node status and for patient characteristics such as age and sex.[4-8] Presently, the most important predictor of outcome for patients with localized melanoma is the presence of regional lymph nodes metastases.[8]

Modern lifestyle changes are causing more people to be obese. Obesity develops gradually and is mostly associated with increased energy intake, especially eating fat and sugars, by eating too much, and by wrong lifestyle choices, such as physical inactivity. The prevalence of obesity has doubled since 1980.[9] In 2016, worldwide, 39% of adults >18 years of age was overweight and 13% obese.[10] In the Netherlands, in 2018, 50,2% percent of the adults is overweight and 15% is obese.[11]

Obesity represents a serious public health problem. It may increase the risk of many health problems, including diabetes, cardiovascular disease and musculoskeletal disorders. Obesity is an established endogenous risk and progression factor associated with significantly higher all-cause mortality.[10] It is also a risk factor for the development of common and less common types of cancer, specifically female breast and ovary, colorectal, uterine corpus, esophagus (adenocarcinoma), pancreatic, kidney (renal cell), liver, stomach (gastric cardia), gallbladder, thyroid, multiple myeloma, and brain (meningioma) cancers.[12] In the USA, 5% of all new cancers in men and 11% in women are attributable to obesity.[13] In contrast to being a risk factor for the development of a variety of cancers, the effect of obesity on survival seems to be more complex. According to the obesity paradox, cancer patients with moderately increased body mass index (BMI) have improved outcomes as compared to those with normal weight whereas morbidly obese cancer patients have decreased outcomes.[14]

The associations between obesity and melanoma risk and outcomes remain unclear. A meta-analysis showed elevated melanoma risk with increasing BMI among men, whereas a pooled case-control study on women resulted in a null association between BMI and melanoma risk.[15,16] As to outcomes, associations between elevated BMI and poorer melanoma patient outcomes have been found; no associations between BMI and melanoma survival were reported; and improved outcomes in male obese metastatic melanoma patients treated with immune or targeted therapy were found, while no significant associations between obesity and outcomes were found in women or in patients receiving chemotherapy.[17-19]

Lack of exercise and physical inactivity are important factors related to obesity.[20] Obesity is more prevalent among those with lower socioeconomic status than among those with higher socioeconomic status.[21] Obesity and social economic status (SES) are found to be negatively associated in melanoma.[22] Additionally, lower SES (measured as lower median household income) melanoma patients presented more often with advanced stages of melanoma and had a shorter survival.[23,24]

Consequently, the aim of the current study was to investigate the impact of obesity at diagnosis on recurrence-free period (RFP), melanoma-specific survival (MSS), and overall survival (OS) in clinical stage IB-II melanoma patients, adjusted for potential tumor and patient-related confounders, specifically: primary tumor site, histology, Breslow thickness, ulceration, mitosis, and sentinel node status, and age, gender, and SES. Our hypothesis is that obesity (BMI>30 kg/m^2) will negatively affect RFP, MSS and OS.

Methods

Patients and procedure

This study, approved by the UMCG Medical Ethics Committee, included all clinical stage IB-II melanoma patients, aged >18 years, who underwent sentinel lymph node biopsy (SLNB) staging between 1995 and 2018 at the Department of Surgical Oncology of the University Medical Center of Groningen (UMCG). Excluded were patients whose BMI could not be calculated because height and/or weight had not been recorded at diagnosis.

Patients with a positive SLNB underwent a completion lymph node dissection. None of the positive sentinel lymph node patients included in the present study received adjuvant systemic treatment (interferon, drug targeted therapy and/or immunotherapy).
Relevant data on tumor and clinicopathologic characteristics (primary tumor site, histology, Breslow thickness, ulceration, mitosis, and sentinel node status) and on patient characteristics (gender, date of birth, body weight, and length) had been prospectively collected and were retrieved from the patients' hospital files.
BMI was calculated as weight (kg) divided by the square of height (m) at the time of the primary diagnosis. Patients were categorized into two groups according to standard WHO definitions in obese (≥30 kg/m^2) or not obese (<30 kg/m^2).
SES scores were assigned to different postal code areas by the Netherlands Institute for Social Research (SCP). SCP based calculations on income, employment and level of education.[25] Calculated scores give an estimate of the SES in the particular postal code area where a patient resides. Calculated SES scores ranged from low (SES=1) to high (SES=5).

Statistical analysis

Statistical analyses were performed using STATA/SE 12.0 (Texas, USA). Patient characteristics were described and comparisons between obese and non-obese patients were performed using Chi-square tests and the median test for age. Cox Proportional Hazards models were used to examine associations between tumor and patient-related variables and recurrence-free period (RFP), and melanoma-specific (MSS) and overall survival (OS). Five-years percentages from the life tables were calculated; univariable and multivariable Hazard Ratios (HR) with corresponding 95% Confidence Interval (95%CI) for the entire follow-up period were assessed. RFP was defined as time from wide excision until recurrence; MSS as time from wide excision until death of melanoma; and OS as time from wide excision until death due to any cause. Of the patients alive and in follow-up, date of wide excision until last outpatient visit was documented as follow-up time. All variables with a p-value<0.05 in univariable analyses and obesity were entered in the multivariable model. Survival curves were generated with the Kaplan-Meier method. P-values <0.05 were considered statistically significant.

Results

Patients

SLNB staging had been performed in 776 patients aged >18 years at the UMCG between 1995 and 2018. BMI of 61 patients could not be calculated because information on length and/or height was not available. Consequently, analyses were performed in 715 patients, 355 (49.7%) were women and 360 men, median age was 55 (range 18.6-89) years. Of the patients, 566 (79.2%) were not obese and 149 (20.8%) were obese. No significant differences in patient and tumor characteristics were found between obese and not obese patients, except for age and ulceration. Not obese patients were significantly younger and fewer had ulceration as compared to obese patients (p=0.008 and p=0.049 respectively) (Table 1).

Recurrence-free period, and melanoma specific and overall survival

Of the 715 patients, 215 (30.1%) had a recurrence of disease (median FU 1595 days, range 0–6128 days, IQR 608–3175 days), 149 (20.8%) died of melanoma (median FU 1931 days, range 0-6529, IQR 953-3443 days), and an additional 45 patients had died of other causes (total number of patients dead n=194 (27.1%), median FU 1931 days, range 0–6529, IQR 953–3443). As we observed no (melanoma related) mortality in patients with a melanoma ≤1.0 mm in the present cohort, we grouped Breslow thickness into two groups, ≤2 mm (combining ≤1.0 and 1.0-2.0) and >2 mm (combining 2.1-4 and >4.0), for survival analyses.

Univariable analyses showed no significant associations between obesity and SES and RFP, MSS and OS, and between histology and MSS. The remaining variables were significantly associated with RFP, MSS and OS (Tables 2-4).

Cox Proportional-Hazards multivariable analyses showed that obesity did not significantly affect RFP (p=0.08; HR=1.39 (0.96-1.96)), MSS (p=0.07; HR=1.48 (0.97-2.25)), and OS (p=0.25; HR=1.25 (0.85-1.85)), although trends towards significance were found for RFP and MSS (Tables 2-4)(Figures 1a, b and c).

Cox multivariable analyses further showed that neither gender nor histology affected RFP, MSS or OS. Significant effects were found for age, tumor location, Breslow thickness, ulceration, mitotic rate, and SLNB status on outcomes, with the exception of Breslow thickness on OS. Patients who are older, have a melanoma on the arm, those who have melanomas thicker than >2.0, ulceration, a mitotic rate of 5 or higher, and those with a positive SLNB status have decreased outcomes as compared to their counterparts (Tables 2-4).

TABLE 1 **Patient and melanoma characteristics of the study group, and of non-obese (BMI<30) and obese patients (BMI>30) at diagnosis, and comparisons between groups**

Characteristics		Total N=715	Low BMI<30 N=566 (79.2%)	High BMI ≥30 n=149 (20.8%)	*p*-value
Sex	Female	355 (49.7)	277 (48.9)	78 (52.3)	0.46
	Male	360 (50.3)	289 (51.1)	71 (47.7)	
Age	Median	55.0	53.7	58.6	0.008
	(range)	(18.6-89.0)	(18.6-89.0)	(22.9-82.8)	
SES	Low (1)	241 (35.2)	186 (34.4)	55 (38.5)	0.61
	2	167 (24.4)	138 (25.5)	29 (20.3)	
	3	121 (17.7)	92 (17.0)	29 (20.3)	
	4	68 (9.9)	55 (10.2)	13 (9.1)	
	High (5)	87 (12.7)	70 (12.9)	17 (11.9)	
Location	Head/neck	105 (14.7)	85 (15.0)	20 (13.4)	0.37
	Trunk	281 (39.3)	227 (40.1)	54 (36.2)	
	Arm	99 (13.8)	72 (12.7)	27 (18.1)	
	Leg	230 (32.2)	182 (32.2)	48 (32.2)	
Histology	SSM	463 (64.7)	367 (64.8)	96 (64.4)	0.99
	Nodular	189 (26.4)	149 (26.3)	40 (26.8)	
	Other	63 (8.8)	50 (8.8)	13 (8.7)	
Breslow	≤1.0	57 (8.0)	46 (8.1)	11 (7.4)	0.72
	1.0 – 2.0	288 (40.3)	231 (40.8)	57 (38.3)	
	2.1 – 4.0	257 (35.9)	204 (36.0)	53 (35.6)	
	>4.0	113 (15.8)	85 (15.0)	28 (18.8)	
Ulceration	No	473 (67.1)	385 (68.9)	88 (60.3)	0.049
	Yes	232 (32.9)	174 (31.1)	58 (39.7)	
Mitotic rate	0 – 1	282 (43.9)	218 (42.9)	64 (47.8)	0.42
	2 – 4	171 (26.7)	141 (27.8)	30 (22.4)	
	5 or higher	189 (29.4)	149 (29.3)	40 (29.8)	
SLNB positive	No	511 (71.5)	409 (72.3)	102 (68.5)	0.36
	Yes	204 (28.5)	157 (27.7)	47 (31.5)	

TABLE 2 **Recurrence Free Period (univariable and multivariable analyses) according to patient and tumour characteristics**

Characteristic		5-yrs RFP	HR (95%CI)	*p*-value	Multivariable HR (95%CI)	*p*-value
Sex	Female	79.8 (74.8-83.9)	Reference		Reference	
	Male	64.5 (58.7-69.6)	1.76 (1.34-2.33)	<0.001	1.37 (0.97-1.93)	0.07
Age			1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.005
Obesity	No	73.1 (68.9-76.9)	Reference		Reference	
	Yes	68.3 (59.4-75.7)	1.25 (0.92-1.72)	0.16	1.37 (0.96-1.96)	0.08
SES	1	73.4 (66.7-79.0)	Reference			
	2	76.6 (68.8-82.6)	0.85 (0.58-1.23)	0.39		
	3	66.5 (56.4-74.8)	1.18 (0.80-1.73)	0.41		
	4	61.3 (46.8-72.8)	1.42 (0.90-2.25)	0.13		
	5	72.0 (60.1-80.9)	0.86 (0.54-1.37)	0.53		
Location	Head/neck	61.3 (49.9-70.8)	Reference		Reference	
	Trunk	69.2 (62.8-74.7)	0.75 (0.51-1.10)	0.15	0.61 (0.38-0.97)	0.04
	Arm	87.4 (78.3-92.9)	0.34 (0.19-0.61)	<0.001	0.25 (0.13-0.49)	<0.001
	Leg	73.7 (67.0-79.2)	0.69 (0.46-1.02)	0.07	0.64 (0.39-1.04)	0.07

TABLE 2 **Continued**

Characteristic		5-yrs RFP	HR (95%CI)	*p*-value	Multivariable HR (95%CI)	*p*-value
Histology	SSM	77.4 (72.8-81.3)	Reference		Reference	
	Nodular	62.5 (54.8-69.2)	1.68 (1.26-2.26)	<0.001	1.08 (0.76-1.55)	0.65
	Other	63.9 (49.1-75.4)	1.68 (1.06-2.62)	0.02	1.52 (0.91-2.55)	0.11
Breslow	≤1.0	98.2 (87.8-99.7)	Reference		Reference	
	1.0 – 2.0	85.9 (80.8-89.7)	8.23 (1.14-59.5)	0.04	5.70 (0.78-41.6)	0.08
	2.1 – 4.0	62.5 (55.8-68.4)	18.56 (2.58-133.2)	0.004	7.53 (1.02-55.4)	0.05
	>4.0	49.3 (39.0-58.8)	29.56 (4.09-213.52)	0.001	8.79 (1.16-66.3)	0.03
Ulceration	No	81.8 (77.5-85.3)	Reference		Reference	
	Yes	53.6 (46.5-60.2)	2.75 (2.09-3.63)	<0.001	2.10 (1.50-2.93)	<0.001
Mitotic rate	0 – 1	84.9 (79.5-89.0)	Reference		Reference	
	2 – 4	77.6 (70.4-83.3)	1.43 (0.96-2.16)	0.08	1.29 (0.84-1.98)	0.24
	5 or higher	56.7 (49.0-63.7)	2.67 (1.86-3.83)	<0.001	1.53 (1.01-2.30)	0.04
SLNB	Negative	80.7 (76.6-84.2)	Reference		Reference	
	Positive	51.3 (43.7-58.3)	3.08 (2.35-4.04)	<0.001	2.83 (2.08-3.87)	<0.001

TABLE 3 **Melanoma Specific Survival (univariable and multivariable analyses) according to patient and tumour characteristics**

Characteristic		5-yrs MSS	HR (95%CI)	*p*-value	Multivariable HR (95%CI)	*p*-value
Sex	Female	88.3 (83.9-91.5)	Reference		Reference	
	Male	76.2 (70.7-80.7)	1.88 (1.34-2.63)	<0.001	1.35 (0.88-2.05)	0.16
Age			1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.002
Obesity	No	82.7 (78.9-85.9)	Reference		Reference	
	Yes	80.4 (72.0-86.5)	1.39 (0.96-2.01)	0.08	1.48 (0.97-2.25)	0.07
SES	1	84.8 (78.9-89.2)	Reference			
	2	83.1 (75.6-88.5)	0.95 (0.60-1.51)	0.84		
	3	78.7 (69.0-85.6)	1.37 (0.87-2.18)	0.17		
	4	77.6 (63.8-86.7)	1.75 (1.01-3.03)	0.05		
	5	82.0 (70.3-89.4)	1.06 (0.61-1.84)	0.82		
Location	Head/neck	74.4 (62.6-83.0)	Reference		Reference	
	Trunk	79.0 (73.1-83.8)	0.81 (0.51-1.29)	0.39	0.57 (0.33-0.96)	0.04
	Arm	90.3 (81.5-95.1)	0.40 (0.20-0.80)	0.009	0.27 (0.13-0.58)	0.001
	Leg	85.6 (79.8-89.9)	0.67 (0.42-1.10)	0.11	0.50 (0.27-0.90)	0.02

TABLE 3 **Continued**

Characteristic		**5-yrs MSS**	**HR (95%CI)**	***p*-value**	**Multivariable HR (95%CI)**	***p*-value**
Histology	SSM	86.2 (82.1-89.5)	Reference			
	Nodular	75.4 (68.0-81.3)	1.40 (0.98-1.99)	0.06		
	Other	74.6 (60.2-84.5)	1.55 (0.92-2.62)	0.09		
Breslow	≤2.0	93.0 (89.0-95.5)	Reference		Reference	
	>2.0	72.8 (67.4-77.4)	2.85 (1.96-4.13)	<0.001	1.64 (1.06-2.54)	0.03
Ulceration	No	89.4 (85.6-92.1)	Reference		Reference	
	Yes	68.3 (61.2-74.3)	2.69 (1.94-3.73)	<0.001	2.06 (1.39-3.02)	<0.001
Mitotic rate	0 – 1	91.0 (85.9-94.3)	Reference		Reference	
	2 – 4	86.1 (79.6-90.6)	1.42 (0.85-2.36)	0.18	1.29 (0.75-2.19)	0.35
	5 or higher	70.8 (63.4-77.0)	2.93 (1.81-4.44)	<0.001	1.83 (1.12-3.00)	0.02
SLNB	Negative	88.5 (85.1-91.4)	Reference		Reference	
	Positive	66.8 (59.0-73.4)	66.8 (59.0-73.4)	<0.001	2.65 (1.84-3.81)	<0.001

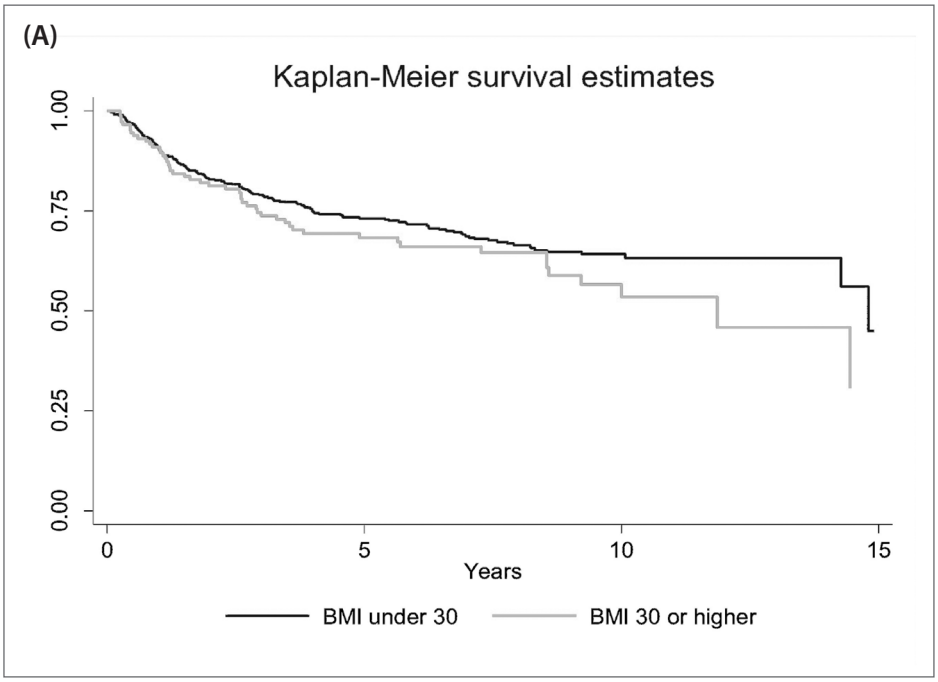
TABLE 4 **Overall Survival (univariable and multivariable analyses) according to patient and tumour characteristics**

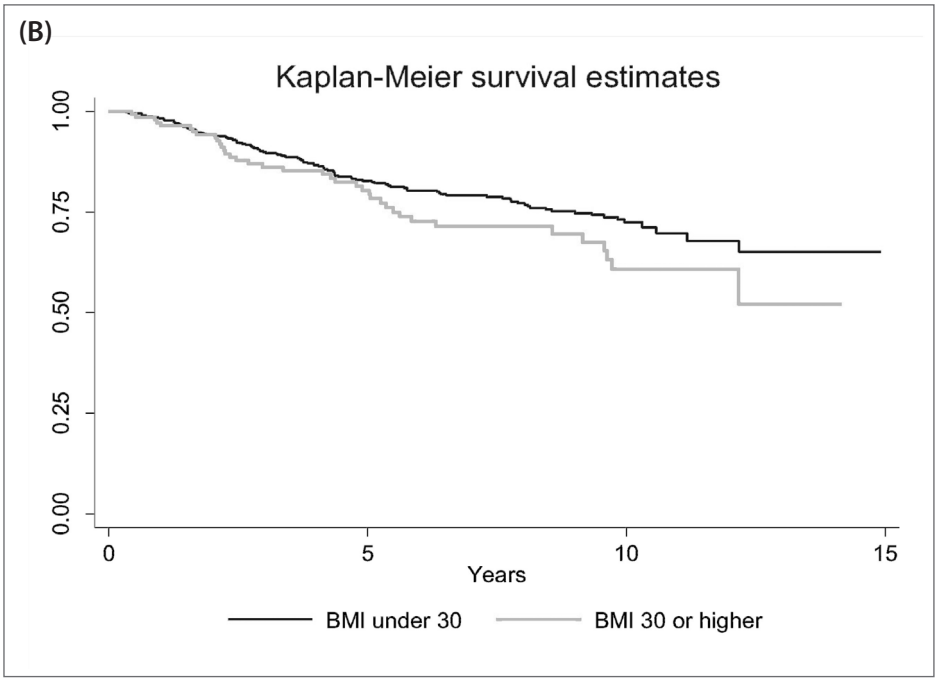
Characteristic		5-yrs OS	HR (95%CI)	*p*-value	Multivariable HR (95%CI)	*p*-value
Sex	Female	85.9 (81.3-89.5)	Reference		Reference	
	Male	71.5 (66.0-76.3)	1.97 (1.46-2.64)	<0.001	1.34 (0.92-1.94)	0.12
Age			1.04 (1.03-1.05)	<0.001	1.03 (1.02-1.05)	<0.001
Obesity	No	78.9 (75.0-82.4)	Reference		Reference	
	Yes	77.3 (68.8-83.8)	1.24 (0.89-1.73)	0.21	1.25 (0.85-1.85)	0.25
SES	1	80.3 (74.1-85.1)	Reference			
	2	78.9 (70.9-84.9)	1.04 (0.70-1.53)	0.85		
	3	75.0 (65.1-82.4)	1.21 (0.80-1.82)	0.37		
	4	73.3 (58.9-83.4)	1.48 (0.89-2.46)	0.13		
	5	81.0 (69.3-88.5)	1.12 (0.70-1.79)	0.63		
Location	Head/neck	68.5 (56.5-77.9)	Reference		Reference	
	Trunk	75.3 (69.1-80.3)	0.79 (0.53-1.19)	0.26	0.66 (0.41-1.08)	0.10
	Arm	87.7 (78.4-93.2)	0.45 (0.29-0.80)	0.006	0.36 (0.19-0.68)	0.002
	Leg	82.7 (76.6-87.3)	0.60 (0.39-0.92)	0.02	0.53 (0.31-0.90)	0.02

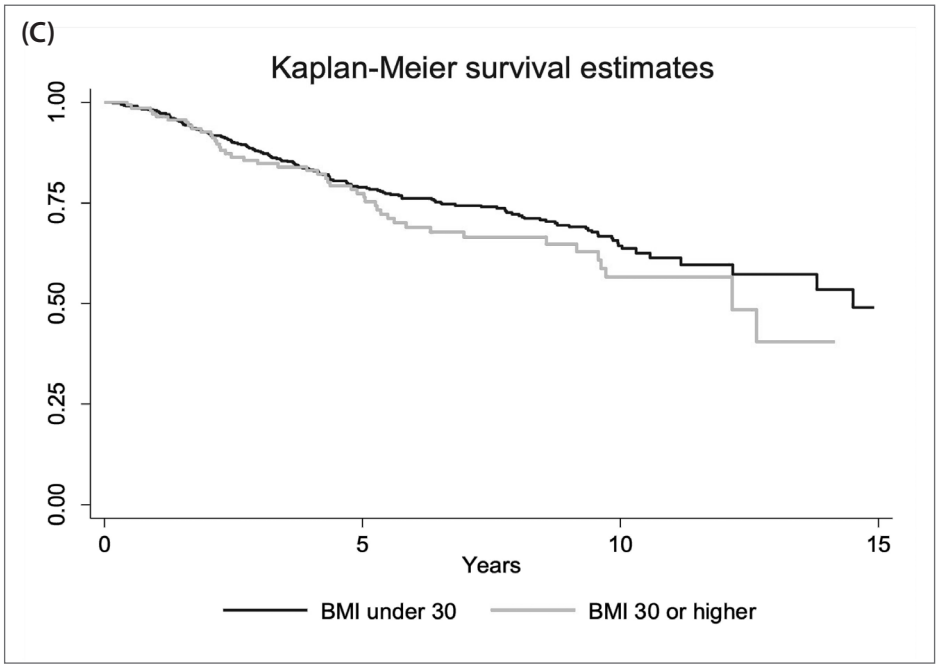
TABLE 4 **Continued**

Characteristic		5-yrs OS	HR (95%CI)	*p*-value	Multivariable HR (95%CI)	*p*-value
Histology	SSM	83.5 (79.2-87.0)	Reference		Reference	
	Nodular	70.1 (62.7-76.4)	1.52 (1.12-2.06)	0.008	1.03 (0.71-1.47)	0.88
	Other	70.8 (56.2-81.3)	1.54 (0.96-2.47)	0.07	1.44 (0.82-2.54)	0.20
Breslow	≤2.0	90.0 (85.5-93.1)	Reference		Reference	
	>2.0	68.8 (63.4-73.6)	2.60 (1.88-3.58)	<0.001	1.47 (0.99-2.20)	0.06
Ulceration	No	86.2 (82.2-89.3)	Reference		Reference	
	Yes	65.0 (58.0-71.2)	2.33 (1.74-3.11)	<0.001	1.72 (1.22-2.42)	0.002
Mitotic rate	0 – 1	88.2 (82.8-92.0)	Reference		Reference	
	2 – 4	83.1 (76.4-88.1)	1.41 (0.91-2.20)	0.12	1.43 (0.90-2.28)	0.13
	5 or higher	66.9 (59.5-73.3)	2.66 (1.80-3.93)	<0.001	1.96 (1.26-3.05)	0.003
SLNB	Negative	85.3 (81.4-88.4)	Reference		Reference	
	Positive	62.6 (55.1-69.5)	2.53 (1.91-3.37)	<0.001	2.38 (1.72-3.30)	<0.001

FIGURE 1 **Kaplan Meier curves (A) RFP, (B) MSS, (C) OS according to obesity**







Discussion

The current study showed that recurrence-free period, melanoma-specific survival and overall survival in stage IB-II melanoma patients were not associated with obesity, defined as BMI >30kg/m^2. However, trends towards significance were strong for RFP and MSS. Additionally, multivariate analyses showed that, of the tumor characteristics, location, Breslow thickness, ulceration, mitotic rate and SLNB status were significantly associated with recurrence-free period, and melanoma-specific and overall survival but histology was not associated with these outcomes. Lastly, of the patient characteristics, age was associated with these three outcomes but no significant associations were found with sex and SES.

The hypothesis we formulated for the present study that obesity would be associated with a decreased RFP, MSS and OS in clinical stage IB-II melanoma patients was rejected. This study showed that obesity was not significantly associated with disease progression and survival. Our results are in line with a study reporting no association between elevated BMI and melanoma mortality, but in contrast to a study reporting poorer disease-free survival in obese than in non-obese patients with stage I-II melanoma, and to a study that found improved outcomes in obese male patients with metastatic melanoma who received targeted or immunotherapy.[17-19] Our study does not support the obesity paradox, a phenomenon that has been criticized before. Methodological (among these are BMI being a suboptimal measure, confounding, selection and detection bias, reverse causality) and/or clinical issues (such as tumor aggressiveness, response to treatment) may explain differences found between studies in the existence of an obesity paradox.[14] As to the clinical issues, obesity induces immune suppression and accelerates tumor growth.[26] When melanoma invades the deeper layers of the skin, papillary or reticular dermis or the subcutis, according to Clark, the melanoma cells come into contact with adipose tissue which secretes both soluble factors and exosomes. This supports melanoma proliferation, invasiveness and metastatic potential.[27] The effect of obesity on melanoma growth patterns, and the impact of obesity on immune responses, in general and in cancer (immuno)therapy, are poorly understood. For metastatic melanoma and others malignancies, a potential correlation between overweight and the efficacy of immune checkpoint inhibitors is documented.[19,28] A melanoma mice model showed that obesity promotes tumor progression and immune dysfunction, in particular through PD-1 up-regulation, and this might be responsible for the improved response to PD-1/PD-L1 inhibition, rather than the previously described obesity paradox.[26,28,29]

In our study, clinical stage IB-II melanoma patients were included but not advanced stage melanoma patients. It may well be that associations between obesity and melanoma progression and survival are different for advanced stage than for early stage melanoma patients.

Associations with recurrence-free period and melanoma-specific survival were near-significant in the current study, suggesting that obese patients may have poorer outcomes. However, obese patients were significantly older and more had ulceration as compared to the non-obese patients. Older age and presence of

ulceration were both found to be significantly associated with poorer outcomes. Had groups been comparable with respect to these two characteristics, results may not even have been near-significant. Conversely, it may be argued that trends towards significance for RPF and MSS were strong considering the number of obese patients and events in the study and the HR and p-values found and that the results of this study are hypothesis generating. Therefore, it is advisable to repeat this study in a large multicenter cohort of clinical stage IB-II melanoma patients while ensuring that groups are comparable in relevant melanoma-related and patient characteristics.

A number of explanations may play a role for the finding of the present study. Melanoma is diagnosed at an earlier age and lower stage than most other malignancies.[30] The treatment of clinical stage IB-II melanoma consists of surgical (re)excision of the tumor and SLNB.[7] Surgery and anesthesia hardly affect the immune system. The only possible factor affecting the immune system in only surgical treated melanoma patients is increasing age.[31] In line with the literature, the present study showed that age was an independent predictor for melanoma progression and survival, and for overall survival. The tumorbiology and/or host immunity is different for melanoma patients in differing ages.[32]

Conform literature, men were found to have decreased outcomes as compared to women in univariate analyses.[33] However, in multivariate analyses results were not significant, indicating that other variables included in the analyses play a greater role in disease progression and survival.

The present study found that SES was not associated with worse outcomes. A study from the Dutch Cancer Registry showed that low SES was associated with advanced melanoma.[34] It may well be that knowledge about the early warning signs of melanoma is more limited in lower than in higher SES people, and that, consequently, lower SES people visit a general practitioner later than higher SES people do. It is reassuring to find that when diagnosed with early stage melanoma, SES does not affect disease outcome. This suggests that medical treatment and financial resources of early stage melanoma patients are independent of SES level in the Netherlands.

The percentage of obese (BMI>30kg/m^2) patients (20,8%) found in the current study is higher than that (15%) found in The Netherlands in 2018.[35] However, the

last percentage is based on self-report while body height and weight from which BMI was calculated in the present study was measured objectively.

A strength of the current study is that a large cohort was included with prospectively collected baseline data on several potential confounders in the relationship between BMI and recurrence-free period, and melanoma-related and overall mortality. Also, body weight and height used to calculate BMI were objectively measured at the time of primary diagnosis. Questionnaire-based self-report is more prone to error. A limitation is that only BMI was used as measure of obesity and not measures such as fat mass and fat-free mass index that may have been more sensitive.[36]

We adjusted for a number of clinicopathological and sociodemographic variables known to affect melanoma progression and survival. Other variables have been found to affect cancer outcomes, such as biomarkers (LDH, S-100B), tumor immune response-related cytokines/chemokines, inflammatory markers (CRP) and smoking behavior.[17,37-40] A relationship has been found between smoking and SLN metastasis in stage IB-II melanoma patients, that is independent of tumor thickness and ulceration.[38] Unfortunately, we were unable to investigate relationships between the just mentioned variables, obesity and disease outcome. Future studies should include such variables in analyses.

Another limitation is that possible effects of changes in adiposity levels prior to and after diagnosis on oncological endpoints could not be examined. It has been shown that changes in adiposity levels affect disease and outcome.[41,42,43] It may be argued that obesity levels would not change during the time of early development of a melanoma, nor following the not so aggressive treatment, namely a surgical intervention, of early stage melanoma.

Conclusion

Obesity (BMI >30kg/m^2) is not significantly associated with recurrence-free period, and melanoma-specific or overall survival in stage IB-II melanoma patients although trends towards significance were found for RFP and MSS. Older melanoma patients have a decreased recurrence-free period, and melanoma-

specific and overall survival. No gender or SES effects were found. Patients with a melanoma on the arm, a thicker melanoma, ulceration, a mitotic rate of >5, and/or a positive sentinel lymph node status have a decreased recurrence-free period, melanoma-specific and overall survival as compared to their counterparts.

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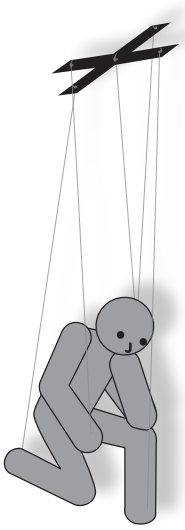
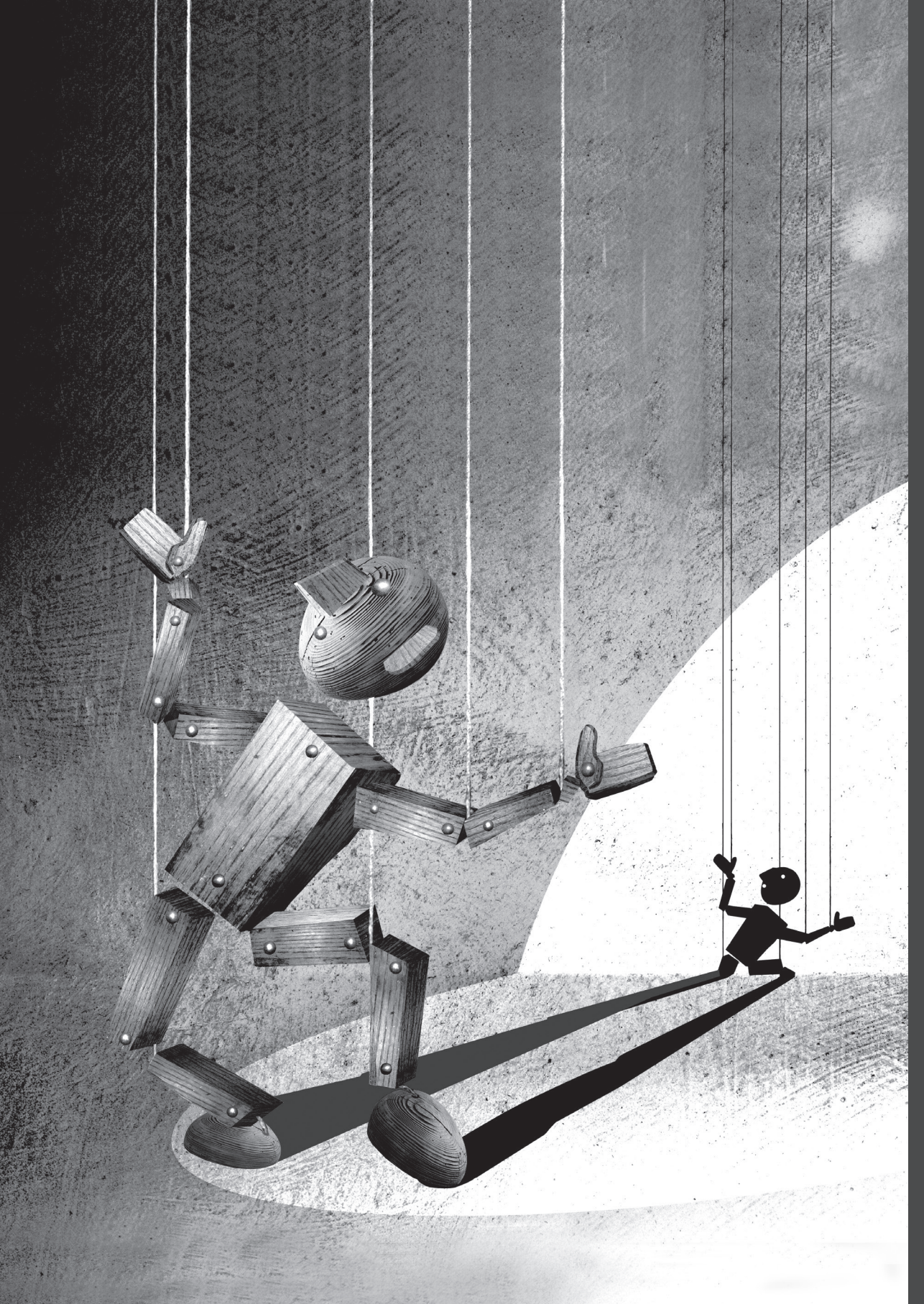
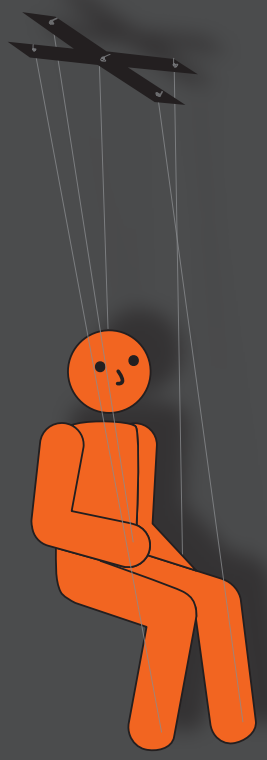




5

S-100B as an extra selection tool for FDG PET/CT scanning in follow-up of AJCC stage III melanoma patients



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Abstract

Background and Objectives
This current study assessed the value of S-100B measurement to guide FDG PET/CT scanning for detecting recurrent disease in stage III melanoma patients.

Methods
This study included 100 stage III melanoma patients in follow-up after curative lymph node dissection. Follow-up visits included physical examination and S-100B monitoring. FDG PET/CT scanning was indicated by clinical symptoms and/or elevated S-100B.

Results
Of 100 patients, 13 (13%) had elevated S-100B without clinical symptoms, of whom 7 (54%) showed disease evidence upon FDG PET/CT scanning. Twenty-six patients (26%) had clinical symptoms with normal S-100B, and FDG PET/CT revealed metastasis in 20 (77%). Three patients had clinical symptoms and elevated S-100B, and FDG PET/CT revealed metastasis in all three (100%). Overall, FDG PET/CT scanning revealed metastasis in 30 of the 42 patients (71.4%). For 7 recurrences, elevated S-100B prompted early detection of asymptomatic disease; 10% of all asymptomatic patients in follow-up, 23% of all patients with recurrent disease.

Conclusion
S-100B cannot exclude recurrent disease during follow-up of stage III melanoma. However, adding S-100B measurement to standard clinical assessment can guide FDG PET/CT scanning for detecting recurrent melanoma.

Introduction

The incidence of cutaneous melanoma has increased worldwide over recent decades.[1] In the Netherlands, 1563 new cases were diagnosed in 1990, and this number grew to 6743 in 2017.[2] Mortality has increased at a lower rate, with 348 melanoma-related deaths in 1990 in the Netherlands, and 767 in 2016. The lower rise in mortality is because the increased incidence largely involves more cases of thin melanoma, likely due to improved awareness and earlier melanoma detection.[1,3]

In melanoma patients, the goal of follow-up surveillance is the cost-effective detection of recurrence at an early stage, based on the assumption that early surgical and/or systemic treatment will improve disease-free survival (DFS), melanoma-specific survival (MSS), and overall survival (OS). There are no clinical data to support this assumption. Until now, data on the effectiveness of routine imaging for recurrence detection in follow-up is limited. Data with respect to an impact on the quality of life in melanoma patients with intensive follow-up schedules are lacking.[4]

The melanoma biomarker S-100B reportedly shows strong correlations with distant-metastasis-free survival and overall survival in stage IIB–III melanoma patients.[5] The serum concentration of S-100B is correlated with disease stage, and S-100B is an independent predictor of melanoma prognosis in patients undergoing therapeutic lymph node dissection (TLND) for nodal macro-metastases.[6,7] German melanoma follow-up guidelines added the melanoma biomarker S-100B and Italian guidelines added both S-100B and FDG PET/CT scanning, in addition to regular patient history and physical examination.[8,9] Specifically, S-100B measurement has been recommended for use in some follow-up guidelines in the selection of stage III patients to undergo FDG PET/CT scanning. However, the added value of this screening is unknown.[10,11] Assessment of the melanoma marker could potentially contribute to the detection of asymptomatic disease recurrence in stage III melanoma, and therewith reduce the number of routine FDG PET/CT scans. As long as scientific data on the effect of standard scanning regimens are lacking, a strategy using a biomarker as a trigger for scanning in asymptomatic patients could be an interesting alternative.

In the present study, we primarily aimed to assess the added value of the biomarker S-100B as a selection tool prior to FDG PET/CT scanning for the detection of recurrent disease in stage III melanoma patients. Our secondary objective was to evaluate the associated costs of this follow-up strategy.

Materials and methods

Patients

This investigation included all patients with stage III melanoma who underwent curative treatment with complete lymph node dissection (CLND) for a positive sentinel node, or with TLND for macro-metastases, and were treated at the Division of Surgical Oncology of the University Medical Center Groningen (UMCG), the Netherlands. The study protocol was applied to all stage III melanoma patients who were in follow-up in 2015, and to all newly diagnosed patients since 2015. Study data were collected during the period 2015–2018. Patients who underwent off-protocol FDG PET/CT imaging during this time period were excluded from the present analysis. Data collection was conducted according to the declaration of Helsinki ethical principles for medical research involving human subjects.[12]

Follow-up

Outpatient follow-up visits included patient medical history, physical examination, and serum S-100B and LDH laboratory testing following the UMCG protocol (Table 1).

TABLE 1 **Follow-up protocol for stage III melanoma at University Medical Center Groningen**

Years of follow-up	Outpatient visit + S-100B measurement
1st year	4× per year
2nd year	3× per year
3rd–5th year	2× per year
>5th year	1× per year

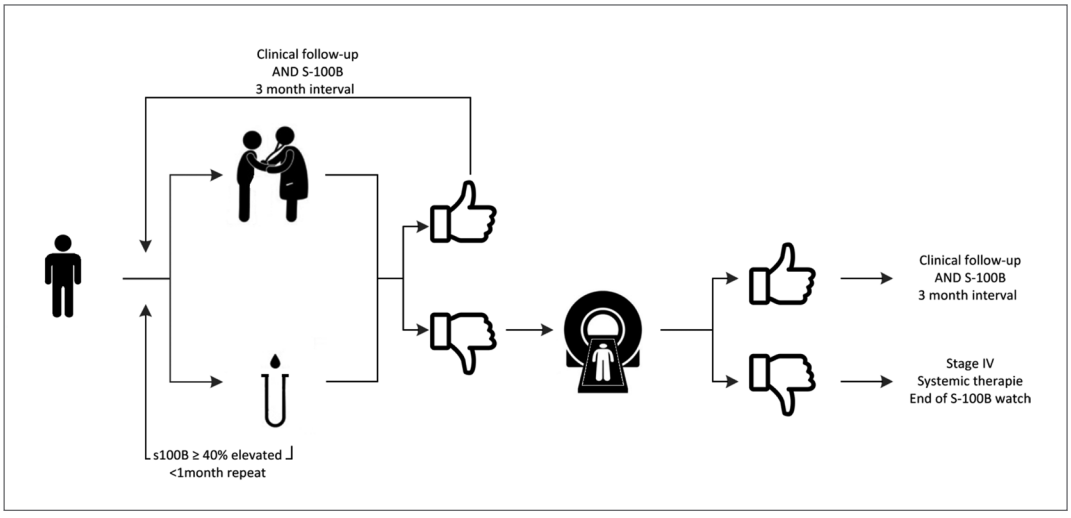
Serum S-100B level laboratory calculations were performed as previously described.[7] The S-100B cut-off value was ≥0.15 µg/L. S-100B level was defined as borderline if it was between 0.10–0.15 µg/L and/or showed a ≥40% elevation compared to the last measurement. A change of ≥40% was considered statistically significant based on the biological and analytical variations of S-100B.[13]

FDG PET/CT scanning was performed in cases with clinical suspicion of recurrent melanoma and/or an elevated S-100B level. In cases with borderline S-100B values, measurement was repeated after four weeks, and FDG PET/CT scanning was performed when S-100B was persistently borderline or elevated (Figure 1). The indication for FDG PET/CT scanning was recorded, and categorized into three groups: 1) clinical symptoms and normal S-100B, 2) clinical symptoms and elevated S-100B, and 3) no clinical symptoms and elevated S-100B.

Costs

For all patients participating in the UMCG follow-up protocol, we calculated the follow-up costs of the detection of asymptomatic and symptomatic recurrences, including S-100B measurement, as well as the total costs of FDG PET/CT scanning. Data were acquired from the Patient Financial Department of the UMCG.

FIGURE 1 **Clinical follow-up and S-100B measurement, 3-month interval**



Results

Patients

A total of 122 patients with stage III melanoma were in follow-up during the study period. The median follow-up after CLND or TLND was 4.7 years (0.7–15.3 years). We excluded 22 patients due to off-protocol FDG PET/CT scanning. Of the remaining 100 patients, 52 were male and 48 were female, and the median age was 57 years (range, 25–89 years) (Table 2). During the study period, the 100 patients attended a total of 456 outpatient visits with corresponding S-100B measurements (Table 3).

Indications for PET/CT

During the 456 outpatient visits, elevated S-100B was found 42 times (9.2%) (Table 3). Of the 100 patients, 58 patients (58%) had no clinical suspicion of recurrence or elevated S-100B level during their follow-up visits, and thus had no indication for FDG PET/CT scanning. The remaining 42 patients (42%) had clinical symptoms and/or elevated S-100B and, therefore an indication for FDG PET/CT scanning. Thirteen patients were asymptomatic but had elevated S-100B levels (in 54% recurrent melanoma on PET/CT). Twenty-six patients presented with clinical symptoms and a normal S-100B level (in 77% recurrence on PET/CT). Three patients had both clinical symptoms and elevated S-100B (100% recurrence on PET/CT) (Table 4).
Of all 100 patients, 26 had symptoms without S-100B elevation, which leaves 74 asymptomatic patients in this cohort. Thirteen of these asymptomatic patients (18%) had elevated S-100B levels and seven (10%) showed recurrent disease on the FDG PET/CT scan.

Yield per PET/CT indication

A total of 42 FDG PET/CT scans were obtained in this study, of which 30 (71%) showed evidence of recurrent disease. Of these 30 disease-revealing FDG PET/CT scans, 7 (23%) were performed based on elevated S-100B levels in asymptomatic patients. The remaining 23 disease-revealing scans were performed based on clinical symptoms (77%), 3 with and 20 without elevated S-100B measurements. Twelve FDG PET/CT scans were negative, 6/29 symptomatic patients (21%)(with and without elevated S-100B) and 6/13 patients with elevated S-100B (46%) (p=0.09) (Table 4, Figure 2).

TABLE 2 **Baseline characteristics of patients in the follow-up cohort**

Characteristic	
Gender	
Female, n (%)	48 (48.0%)
Male, n (%)	52 (52.0%)
Years of age, median (range)	57 (25–89)
Primary melanoma site, n (%)	
Head	4 (4%)
Trunk/back	36 (36%)
Lower extremity	41 (41%)
Upper extremity	15 (15%)
Unknown primary	4 (4%)
Breslow thickness in mm, median (range)	2.0 (0.4–14.0)
Ulceration	
Yes	32 (32%)
No	52 (52%)
Sentinel Node Performed	
Yes	69 (69%)
No	26 (26%)
Sentinel Node Positive	
Yes	65 (94%)
No	4 (6%)
Lymph Node Dissection	
CLND[a]	43 (43%)
TLND[b]	36 (36%)
Type of melanoma, n (%)	
Superficial spreading	64 (64%)
Nodular melanoma	21 (21%)
Verrucous nevoid melanoma	1 (1%)
Spitzoid melanoma	1 (1%)
Other[c]	13 (13%)

[a]*CLND* Completion Lymph Node Dissection; [b]*TLND* Therapeutic Lymph Node Dissection; [C]Not specified

TABLE 3 **Overview of follow-up visits, S-100B tests, and FDG PET/CT scans**

Patient assessment	
Years of follow-up, median (range)	4.7 (0.7–15.3)
S-100B samples, N	456
Normal, n (%)	414 (90.8%)
Elevated[a], n (%)	42 (9.2%)
Indication for FDG PET/CT scan, n (%)	
Symptoms	26 (62%)
Symptoms + elevated S-100B	3 (7.1%)
Elevated s-100B	10 (23.8%)
S-100B level elevation ≥40%	3 (7.1%)
Total FDG PET/CT scans*, n	42
Positive FDG PET/CT scans, n (%)	30 (71.4%)
Negative FDG PET/CT scans, n (%)	12 (28.6%)

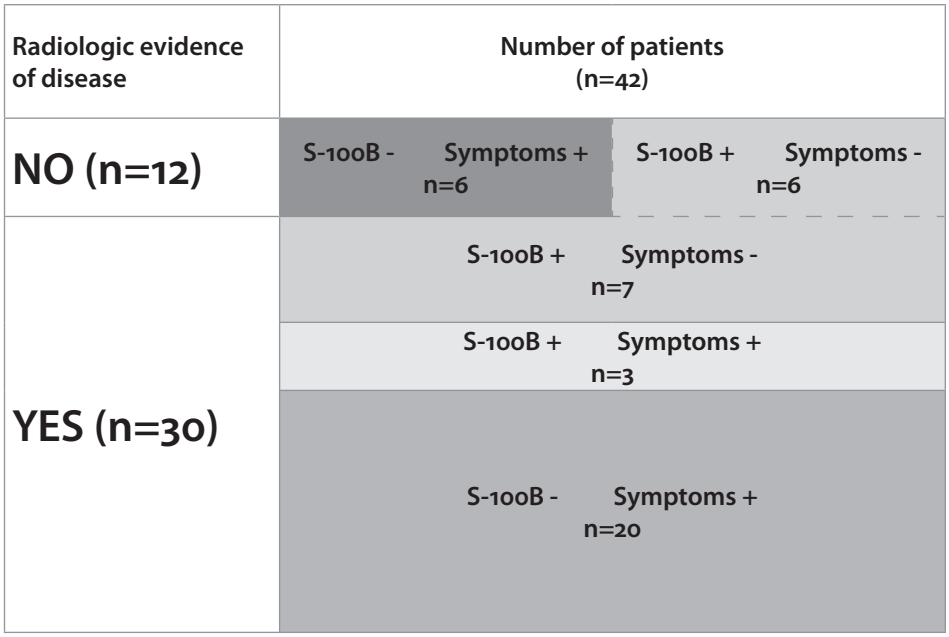
FDG fluorodeoxyglucose; *PET/CT* positron emission tomography/computed tomography
[a]All elevated S-100B samples, including repeated measurements from a single patient in cases showing a S-100B elevation of ≥40%
*One FDG PET/CT scan per patient; additional scans performed after one positive FDG PET/CT scan were not counted

TABLE 4 **Indications for FDG PET/CT scanning and their association with recurrent disease**

	Positive FDG PET/CT scan (n=30)		**Negative FDG PET/CT scan (n=12)**	
Indication for FDG PET/CT scan		**Symptomatic vs asymptomatic**		**Symptomatic vs asymptomatic**
Symptoms (n=26)	20 (76.9%)	23 (77%)	6 (23.1%)	6 (50%)
Symptoms + S-100B (n=3)	3 (100%)		0 (0%)	
Elevated S-100B (n=13)	7 (53.8%)	7 (23%)	6 (46.2%)	6 (50%)

FDG fluorodeoxyglucose; *PET/CT* positron emission tomography/computed tomography

FIGURE 2 **PET outcome proportionally classified for indication for 42 of 100 scanned patients**



Stage and recurrence pattern

Of the 30 disease-revealing FDG PET/CT scans, 15 patients were initially diagnosed with (AJCC version 8) stage IIIA disease, 8 with stage IIIB, 5 with stage IIIC and 2 with stage IIID. The 12 negative FDG PET/CT scans included 2 stage IIIA, 7 stage IIIB and 3 stage IIIC patients.

Differences in recurrence pattern were found for the 20 symptomatic and the 7 asymptomatic patients. Of the 20 symptomatic patients, 12 (60%) presented with locoregional recurrences, 5 (25%) with distant recurrences and 3 (15%) with both locoregional and distant recurrences. For asymptomatic patients scanned for high S-100B, 5 of 7 patients (71.4%) had distant and 2 patients (28.6%) locoregional metastases.

Costs

The total S-100B laboratory costs and the costs of FDG PET/CT scanning for all 100 stage III melanoma patients undergoing follow-up under the UMCG protocol were calculated. In 2015, the cost of processing a single S-100B sample was € 109,-, and the cost of a FDG PET/CT scan was € 913,-. The total cost was € 88.050,- for all S-100B samples (456 in total) processed during follow-up of 100 patients plus the cost of the 42 FDG PET/CT scans.

When a standard scan protocol (e.g. as suggested in the TRIM study (NCT03116412)) is applied to the same cohort with corresponding follow-up and costs as in the current study, total diagnostic costs (FDG PET/CT and S-100B) would have been €408.800,- (100 patients in follow-up with S-100B and FDG PET/CT at baseline, 86 patients at 6 months, 78 patients at 12 months, 69 patients at 24 months and 67 patients at 36 months).

Discussion

The present study evaluated the tumor marker S-100B in stage III melanoma patients as an additional tool to guide FDG PET/CT scanning for the detection of recurrent disease. Of all S-100B measurements, 2.9% eventually led to FDG PET/CT scanning. However, S-100B was the only trigger for the FDG PET/CT scan in 23% of all patients in whom recurrent disease was detected. For all asymptomatic patients in follow-up, S-100B measurement led to the discovery of recurrent disease in 10% of them. Clearly, S-100B measurement cannot exclude disease during follow-up of stage III melanoma. However, our findings show that the tumor marker can serve as an extra tool, in addition to standard clinical assessment, to guide FDG PET/CT scanning for the detection of recurrent disease, without the financial, logistical, and radiation burdens of a standard scanning follow-up scheme.

In cases of cutaneous melanoma, S-100B serum concentrations are a prognostic marker of metastatic disease.[5,7] Serum concentrations of S-100B correlate with disease stage, although large variation is observed with or without S-100B elevation.[6] Previous findings suggest that S-100B levels may be influenced by the melanoma metastasis location and by variations in the ability of melanoma cells to produce S-100B.[14-16] Together with the limited S-100B elevation in patients with low tumor load, it is difficult to designate S-100B as a solid indicator of recurrence.[17]

In the current study, disease recurrence was detected on FDG PET/CT scans that were performed in 7 patients (23%) with elevated S-100B and no clinical symptoms, in 3 patients (10%) with clinical symptoms and elevated S-100B, and in 20 patients (67%) with clinical symptoms and normal S-100B. These data correspond with previous findings that elevated S-100B was the only sign in 20% of patients with disease progression.[16] In the present series, 33% of patients that recurred IV disease had increased S-100B, which is in line with prior reports of increased S-100B levels in 4–100% of patients with stage IV disease.[6] In stage II and III melanoma patients, the reported sensitivity and specificity of S-100B for recurrent disease varies from 29–43% and 93–94%, respectively.[7,11,18]

To compare with other tumor markers, the widely accepted colorectal cancer biomarker carcino-embryonic antigen (CEA) has a 41–97% sensitivity, which is somewhat higher, and a 52–100% specificity, which is comparable to that of S-100B.[19] A recent study revealed that 1.5% of all CEA measurements from curatively treated patients with stage I–III colorectal cancer ultimately led to recurrence detection.[20,21] As with S-100B, a normal CEA level does not exclude recurrent disease.[22]

Tumor markers can be used in cancer detection and diagnosis, but are mainly used in follow-up to detect recurrent disease in an early phase.[23] The recent development of successful systemic treatment options for stage IV melanoma have given rise to a greater need for early detection of recurrence. It remains unclear whether earlier diagnosis and treatment of stage IV disease with immune or targeted therapy further contributes to improved MSS and OS rates, as lead time bias may occur.[24,25] Recent literature suggests a routine sub-stage-III-specific FDG PET/CT schedule for asymptomatic detection of recurrences. However, the same lead time bias argument as for biomarkers might be applicable.[26] A randomized trial is required to determine whether the gained time reflects real survival time or just earlier knowledge of disease. At the present time, it is clear that adjuvant therapy has advantages over therapies in metastatic settings, and that more durable responses and improved long-term survival are observed with low tumor load.[27-30]

The Swedish Melanoma Study Group has initiated a trial investigating the effectiveness of standard imaging in Sweden (TRIM study; NCT03116412). This prospective randomized multicenter study of the roles of imaging and laboratory testing during follow-up after radical surgery of stage IIB–III melanoma was proposed in 2017, with OS as the study endpoint. Based on the scheduled outpatient

visits, with corresponding FDG PET/CT scans (€ 913,-) and S-100B samples (€ 109,-), the follow-up costs for 100 patients using the TRIM protocol would be € 408.800,-, compared to the cost of € 88.050,- in our current study. Compared to the UMCG protocol applied in our present study, the standard scanning proposed in the TRIM study might lead to earlier detection of metastases, but would also greatly increase melanoma follow-up costs and the radiation burden. Moreover, the additional scans would lead to incidental findings not contributing to melanoma treatment or disease-related survival.[31] The current study protocol could reduce FDG PET/CT scans in asymptomatic melanoma patients, thereby reducing their radiation exposure and the total follow-up costs compared to a standard scanning protocol. However, one must be aware that normal S-100B levels do not exclude metastatic disease, emphasizing the importance of thorough self-inspection by patients and physical examination during follow-up visits.

There are guidelines, based on AJCC version 8, that advice stage IIIC and IIID often receive routine scans, sometimes even stage IIIB.[11,32] Most patients, who have undergone a FDG PET/CT scan in this study were stage IIIA or IIIB. This means using S-100B in selecting for FDG PET/CT scan results in a more refined follow-up system.

This study has limitations. First, most patients were included retrospectively and on-protocol follow-up was 3 years as the median follow-up since stage III diagnosis was 4.7 years. This makes the population more heterogeneous and might influence the recurrence risk. It could be one reason for the slightly lower number of recurrences (30%) than the 38% reported in a recent published study that used routine, sub-stage-specific stage III PET/CT scanning schedule.[26] Secondly, the present study cannot determine the exact survival gain associated with earlier stage IV diagnosis, or the effect of lead time bias. In addition, it is difficult to define what the exact gained S-100B detection percentage is. When the detection rate is calculated over all followed asymptomatic stage III patients the percentage would be 10% (7/71). However, a biomarker can never detect recurrent disease in those patients that in fact do not have a recurrence. When the gain is calculated for the patients that during this study proved recurr (n=30), this number is 23% (7/30), which could be an overestimation because there might still have been patients is the study follow-up with occult recurrent disease.

Therefore, we conclude that the addition of S-100B measurement in the follow-up of stage III melanoma prompted detection of stage IV disease in 10% of all asymptomatic stage III patients, and resulted in 23% additional upstaging. Without the use of S-100B there would have been no indication for FDG PET/CT scanning in this 10% of asymptomatic patients, and 23% of all recurrences would have been found later. In an era with expanding possibilities for systemic melanoma treatment and where routine scanning is a contested practice, there is growing demand for earlier stage IV diagnosis. Adding S-100B measurement to follow-up could be a way to support this demand, when patients are still asymptomatic. Future research is needed to optimize its use, to assess the absolute survival gain, and compare to the efficacy and costs of this follow-up method with those of standard scanning protocols. Research should also focus in the future on patient and tumor characteristics that may predict the sensitivity of S-100B during follow-up, with the aim of identifying patient subgroups in which S-100B shows higher sensitivity, to maximize the effectiveness of this tool.

Conclusions

S-100B cannot exclude recurrent disease during follow-up of stage III melanoma. However, adding S-100B measurement to standard clinical assessment can effectively guide FDG PET/CT scanning for detecting recurrent melanoma. Future studies are needed to determine whether this protocol is a good alternative to follow-up regimens that include standard scheduled FDG PET/CT scans.

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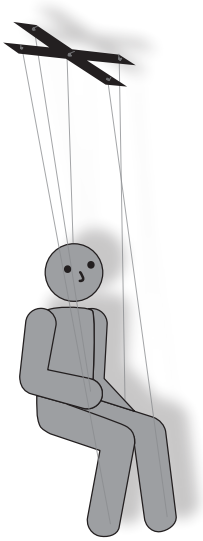

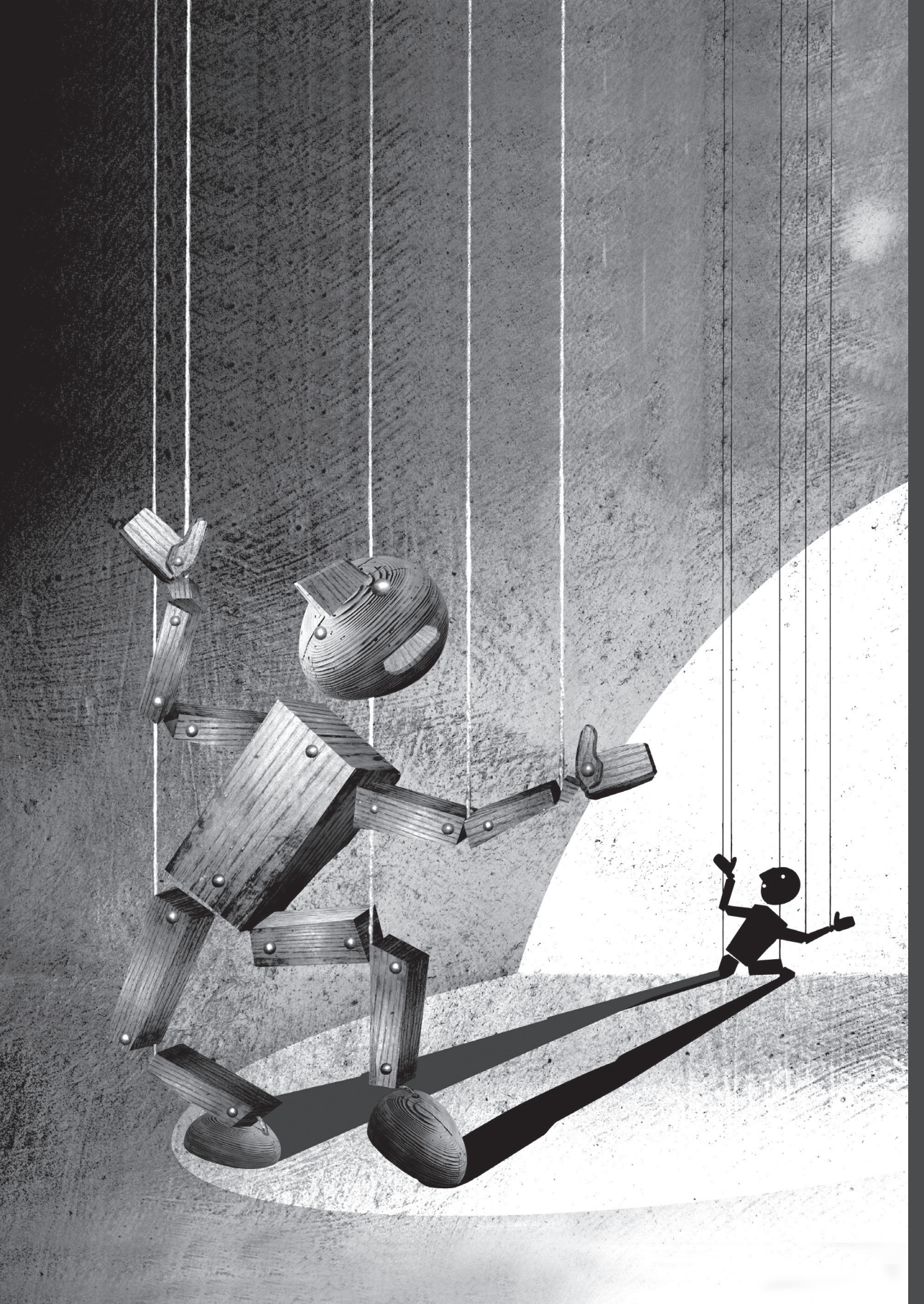

6

The association between active tumor volume, total lesion glycolysis and levels of S-100B and LDH in stage IV melanoma patients

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Abstract

Introduction

The Standardized Uptake Value (SUV) in single lesions on ^{18}F-FDG PET/CT scans and serum S-100B concentrations are inversely associated with disease-free survival in stage IV melanoma. The aim of this study was to assess the association between biomarkers (S-100B, LDH) and the PET-derived metrics $SUV_{mean/max}$, metabolic active tumor volume (MATV), and total lesion glycolysis (TLG) in stage IV melanoma in order to understand what these biomarkers reflect and their possible utility for follow-up.

Methods

In 52 stage IV patients the association between PET-derived metrics and the biomarkers S-100B and LDH was assessed and the impact on survival analyzed.

Results

S-100B was elevated (>0.15 µg/l) in 37 patients (71%), LDH in 11 (21%). There was a correlation between S-100B and LDH (R^2=0.19). S-100B was correlated to both MATV (R^2=0.375) and TLG (R^2=0.352), but LDH was not. Higher MATV and TLG levels were found in patients with elevated S-100B (p<0.001) and also in patients with elevated LDH (>250 U/l)(p<0.001). There was no association between the biomarkers and $SUV_{mean/max}$. Survival analysis indicated that LDH was the only predictor of melanoma-specific survival.

Conclusion

In newly diagnosed stage IV melanoma patients S-100B correlates with ^{18}F-FDG PET/CT derived MATV and TLG in contrast to LDH, is more often elevated than LDH (71% vs. 21%) and seems to be a better predictor of disease load and disease progression. However, elevated LDH is the only predictor for survival. The biomarkers, S-100B and LDH appear to describe different aspects of the extent of metastatic disease and of tumornecrosis.

Introduction

The introduction of effective systemic treatment options (BRAF/MEK inhibitors and immunotherapy) over the past decade has resulted in improved survival rates for stage IV melanoma patients with non-resectable disease.[1,2] Potentially curative surgery is achievable in less than 10% of stage IV patients with metastatic disease, and systemic therapies are most effective when the tumor burden is still low.[3,4] This has resulted in an increased urgency to identify recurrent disease in the follow-up of melanoma patients, especially those with stage III disease in whom the risk of recurrence in the first five years has been reported to be 19%, 36%, 55% and 90% for stage III A, B, C and D (AJCC 8th edition).[5] In order to maximize stage IV treatment efficacy, stage III follow-up strategies are compared, tested, and may be updated in the future by adding biomarkers and/or standard radiological assessments with whole-body Computed Tomography (CT) or ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET scans). For example, in the prospective randomized TRIM study (NCT03116412) the role of imaging with PET/CT or CT scanning and laboratory tests (S-100B, ALP, LDH, and transaminases) during follow-up after radical surgery for stage IIB-C and III melanoma is being assessed.

Globally, there is no consensus in relation to the use of biomarkers in the follow-up of melanoma patients. The German and Swiss guidelines on melanoma follow-up and response evaluation do recommend monitoring of biomarkers (e.g. LDH, S-100B) as well as regular imaging (e.g. ^{18}F-FDG PET/CT) for surveillance.[6,7] In contrast, the NCCN and Australian guidelines do not recommend monitoring of biomarkers, because of insufficient evidence supporting the use of biomarkers in melanoma follow-up.[8,9]

For S-100B, it has been shown that serum levels are correlated with melanoma stage.[10-12] Furthermore, S-100B has proved to be of prognostic significance in stage III patients and can be used as a selection tool for ^{18}F-FDG scanning.[13,14] Serum LDH is used as a biomarker together with ^{18}F-FDG PET/CT in evaluating the response of systemically treated stage IV melanoma patients and predicts the success of systemic ipilimumab therapy before the initiation of treatment. Stage IV patients with ≥2x the upper limit of normal LDH levels do not benefit from ipilimumab treatment in terms of survival and therefore, are not offered this treatment.[15]

The abovementioned associations between LDH and S-100B with melanoma stage and behavior suggest that there is an association between melanoma

biomarkers and active melanoma tumor load. The extent of disease in stage IV melanoma patients is best determined by whole-body ^{18}F-FDG PET/CT, which reveals different metrics reflecting physical tumor volume (metabolic active tumor volume (MATV)), biological tumor activity ($SUV_{mean/max}$ and total lesion glycolysis (TLG=MATV x SUV_{mean})).
The aim of the present study was to provide new insights into the role of biomarkers in the follow-up of melanoma patients, by studying the associations between the biomarkers S-100B and LDH and ^{18}F-FDG PET/CT-derived metrics (i.e. MATV, $SUV_{mean/max}$ and TLG) in melanoma patients with newly diagnosed stage IV disease. Unraveling these associations could lead to a better understanding of what these markers reflect and whether and, if so, how they can be useful in melanoma follow-up.

Methods

Study population
This retrospective study included data for all newly diagnosed stage IV melanoma patients that were retrieved from a prospectively-collected cohort database at the Department of Surgical Oncology of the University Medical Center Groningen (UMCG).

Selected patients (n=60) were >18 years of age with histologically-proven stage IV cutaneous melanoma according to the American Joint Committee on Cancer (AJCC) 8th edition[16-18], with a baseline ^{18}F-FDG PET/CT scan performed between 2010-2015, and S-100B and LDH blood samples taken prior to (median of 1 week; interquartile range (IQR) 0.5-1.5) or just after the ^{18}F-FDG PET/CT scan (median of 2 weeks, IQR 1-3). Patients were excluded if there were multiple small metastases in a single organ (e.g. liver, lung) that made proper analysis impossible (n=3), or if there was no adherence to the European Association of Nuclear Medicine (EANM) ^{18}F-FDG PET/CT scan protocol (n=5).[19,20] Final analyses were performed on 52 patients.

Patient- and tumor characteristics including sex, age, Breslow thickness, site of the primary melanoma, melanoma type and ulceration were collected from medical records, as well as the laboratory results for serum S-100B and LDH (Table 1).

TABLE 1 **Patient and tumor characteristics**

Characteristics		**All patients, N=52**
Sex	Male	30 (58)
	Female	22 (42)
Age (years) at diagnosis		64 [53; 69]
Breslow (mm)		2.8 [1.65; 4.75]
Region primary	Head/Neck	8 (15)
	Trunk	25 (48)
	Lower extremity	16 (31)
	Upper extremity	3 (6)
Melanoma type	Superficial spreading	28 (65)
	Nodulair	14 (33)
	Other	1 (2)
	Missing	9
Ulceration	Yes	16 (40)
	No	24 (60)
	Missing	12
BRAF mutation	Yes	26 (55.3)
	No	21 (44.7)
	Missing	5
S-100B[a]	Elevated	37 (71)
	Normal	12 (29)
LDH[b]	Elevated	11 (21)
	Normal	41 (79)

Data are displayed as n (%) or median [interquartile range]
LDH lactate dehydrogenase
[a] S-100B values >0.15 µg/l are considered elevated
[b] LDH values >250 U/l are considered elevated
All blood samples were taken prior to or just after ^{18}F-FDG PET/CT scan

Data collection was conducted according to the declaration of Helsinki ethical principles for medical research involving human subjects.[21] The Medical Ethics Review Board of the University Medical Center Groningen (METc UMCG) approved the study (METc 2019/515, Research Register number 201900627).

^{18}F-FDG PET/CT and delineation technique

^{18}F-FDG PET/CT scans were performed and reconstructed according to the EANM procedure guideline[19,20] using a hybrid PET/CT scanner (Siemens Biograph mCT 40 and 64 slices). Both systems were from the same vendor and from the same generation; the acquisition and reconstruction protocols were harmonized, and the systems were cross-calibrated. Patients were advised to fast for at least 4-6 h prior to scanning. One hour prior to the PET/CT, patients were injected with ^{18}F-FDG (3 MBq/kg). For the imaging, patients were examined in the supine position and scanned for 1-3 minutes per bed position based on their body weight.

A delineation analysis software program developed in-house (ACCURATE) was used to determine the ^{18}F-FDG PET/CT-derived metrics.[22] All lesions that could not be attributed to physiological uptake of ^{18}F-FDG were assumed to be metastases. This was double-checked with the documentation of the nuclear physician and radiologist. Volumes of interest (VOIs) were automatically drawn using 50% of the SUV_{peak} contour, corrected for local background.[23] For each patient, and for every metastatic lesion, 5 metabolic parameters were extracted: SUV_{mean}, SUV_{max} (voxel with the highest SUV value), the SUV_{peak} (using a 1mL sphere containing the highest average value), Metabolically Active Tumor Volume (MATV), and Total Lesion Glycolysis (TLG; the product of SUV_{mean} and MATV).[24,25] All parameters were corrected for Lean Body Mass (LBM) as recommended by Boellaard et al.[20], using Janmahasatian's formula.[26] For SUV metrics the median and maximum values for all the patient's lesions were calculated. For example, if a patient has four lesions, the SUV_{peak} was calculated for each individual lesion, then the median SUV_{peak} was calculated from these four SUV_{peak} values. For MATV and TLG, when there was more than one lesion, values were summed. All the metrics were log-transformed to approximate a normal distribution.

Statistical analysis

Variables were summarized with frequencies and percentages, with median and interquartile range (IQR) for continuous variables or, when normally distributed, with mean ± SEM. Inferential statistics were performed using Fisher's exact, Mann-Whitney U or T-tests as appropriate to compare variables. The relationship between the ^{18}F-FDG PET/CT-derived metrics and the biomarkers S-100B and LDH were assessed using scatter plots and Pearson correlation.
Receiver operating characteristic (ROC) curves were used to explore the relationship between patient survival and the biomarkers S-100B and LDH.

S-100B and LDH levels per patient were categorized as normal (S-100B<0.15µg/l and LDH<250U/l) or elevated (S-100B>0.15µg/l and LDH>250U/l). Kaplan Meier curves were then constructed describing the melanoma-specific survival, defined as the time from stage IV melanoma diagnosis until last follow-up visit or death. The log-rank test was used for statistical comparison of the groups. For all statistics, a *p*-value <0.05 was considered statistically significant, without correction for multiple comparisons. SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) was used for statistical analyses.

Results

Population

Of the 52 patients with newly diagnosed stage IV melanoma 30 were male (58%) and 22 female (42%) with a median age of 64 years [IQR 53; 69]. The median Breslow thickness of their primary melanomas was 2.8 mm [IQR 1.65; 4.75]. The melanomas were located on the trunk in 25 patients (48%), followed by a lower extremity in 16 (31%), the head/neck region 8 (15%) and an upper extremity 3 (6%). BRAF mutation was present in 26 patients (55%). Twenty-eight melanomas were of the superficial spreading type (65%) and 16 were ulcerated (40%). The biomarker S-100B was elevated in 37 (71%) and LDH in 11 (21%) at the time of the initial diagnosis of stage IV disease (Table 1). All patients with an elevated LDH had elevated S-100B levels simultaneously. The total number of metastatic lesions per patient ranged from 1-66. The median number of lesions per patient was 8 [IQR 3; 14](Appendix A).

For S-100B, there were no patient or tumor characteristics that showed an association with elevated serum levels (Table 2). For LDH, older patients (≥65 years) had more frequently elevated LDH values: 32% versus 12.5% for younger patients (<45 years)(p=0.048). Patients who were BRAF-negative more frequently had an elevated LDH compared to BRAF positive-patients (38.1% vs 11.5% (p=0.043)). The other factors did not show an association with LDH levels (Table 2).

Correlation between biomarkers and ^{18}F-FDG PET/CT-derived metrics

The correlation between LDH and S-100B was R^2=0.191. The R^2 between S-100B and the ^{18}F-FDG PET/CT-derived metrics (SUV_{mean}, MATV and TLG) was R^2=0.019, R^2=0.374 and R^2=0.351 respectively. Both MATV and TLG were significantly correlated (p≤0.01). No significant correlation was found for the ^{18}F-FDG PET/CT-derived metrics (SUV_{mean}, MATV and TLG) and the biomarker LDH with R^2=0.046, R^2=0.025 and R^2=0.019 respectively. The associations between LDH and S-100B, and MATV and S-100B are displayed in Figure 1 and Figure 2. A complete overview of all the correlations between the biomakers LDH and S-100B and the ^{18}F-FDG PET/CT-derived metrics are shown in Table 3 and Appendix B.

ROC analysis of the relationship between survival and biomarker elevation

ROC analysis showed an AUC of 0.563 for S-100B, and 0.693 for LDH (Figure 3).

Melanoma-specific survival

The 52 patients in this cohort had a median follow-up of 24.9 months (range 2.6-86.0). Of these patients, 33 (63%) died of melanoma, and 4 of other causes (3 of an unknown cause and 1 of pleomorphic sarcoma). Median survival for patients with normal LDH (<250U/l) was 28.9 months [IQR 13.5; 45.8] vs. 6.7 months [IQR 4.3; 37.3] for patients with an elevated LDH (>250U/l)(p=0.019). Median survival for patients with normal S-100B (<0.15µg/l) was 23.0 months [IQR 11.9; 42.8] vs. 26.1 months [IQR 6.7; 45.1] for patients with an elevated S-100B (>0.15µg/l)(p=0.709). Kaplan Meier analyses showed that an elevated LDH values (LDH>250U/l) was significantly associated with shorter melanoma-specific survival (p=0.026). However, classification of patients based on a normal (<0.15µg/l) or elevated (>0.15µg/l) level of S-100B was not associated with different survival (Figures 4a and 4b).

Discussion

The goal of the study was to clarify the association between the biomarkers, S-100B and LDH, and tumor load in patients with newly stage IV melanoma, and to re-assess the value of these biomarkers in follow-up. We found a correlation between the values of both biomarkers (S-100B and LDH), while the ^{18}F-FDG PET/CT-derived metrics MATV and TLG were found to be correlated only with S-100B and not with LDH. S-100B was elevated in 71% and LDH in 21% of the newly-diagnosed stage IV melanoma patients, with all patients having an elevated LDH also having an elevated S-100B levels. However, LDH seemed to be the best predictor of survival. An explanation could be that S-100B and LDH describe different aspects of the lesion. When LDH eventually becomes elevated, the disease is already at a further stage of progression, with some tumor necrosis and the prognosis is worse. It might be that S-100B is already elevated in an earlier stage of disease when there is no tumor necrosis. So, S-100B seems to be more a disease proliferation marker and LDH a reflection of tumor necrosis.

An association between the biomarker S-100B and tumor load has previously been suggested by others.[12,27] However, in most of these studies the melanoma stage was used to estimate tumor load. Previous studies of the use of biomarkers including S-100B and LDH for melanoma follow-up have suggested that S-100B, in particular, might be associated with tumor load and could, therefore, be useful in follow-up to detect recurrences in asymptomatic patients.[12,14,28-32] However, there were frequent false-positive and false-negative measurements.

^{18}F-FDG PET/CT is today's most accurate imaging modality for metastatic staging in melanoma combining the diagnostic possibilities of ^{18}F-FDG PET and CT.[33,34] The advantage of the combination is that it provides both metabolic and morphologic information. Beside this, it has also been suggested that the use of both SUV and MATV combined (TLG) could be of prognostic value.[20,35] However, subtraction of these data from scans is a time-consuming process. In the near future (semi-)automatic tumor selection and quantification might be possible and is a prerequisite for further implementation into clinical routine praxis.

TABLE 2 **Disease-related characteristics, stratified by S-100B (S-100B normal/S-100B elevated) or LDH (LDH normal/LDH elevated)**

Characteristics		**N**	**S-100B<0.15 N=15**	**S-100B>0.15 N=37**	***p*-value**	**LDH<250 N=41**	**LDH>250 N=11**	***p*-value**
Sex	Male	30	9 (30)	21 (70)	1.000^	25 (83.3)	5 (16.7)	0.495^
	Female	22	6 (27.3)	16 (72.7)		16 (72.7)	6 (27.3)	
Age (years)	<45	8	3 (37.5)	5 (62.5)	0.414^	7 (87.5)	1 (12.5)	0.199^
	45-64	19	7 (36.8)	12 (63.2)		17 (89.5)	2 (10.5)	
	≥64	25	5 (20)	20 (80)		17 (68)	8 (32)	
	Median [IQR]		62 [47; 67]	65 [54; 71]	0.192#	62 [51; 68]	69 [62; 74]	**0.048#**
Breslow (mm)	<2,00	18	5 (27.8)	13 (72.2)	1.000^	14 (77.8)	4 (22.2)	1.000^
	≥2,00	27	8 (29.6)	19 (70.4)		21 (77.8)	6 (22.2)	
	Missing	7	2	5		6	1	
	Median [IQR]		3.3 [1.4; 4.3]	2.7 [1.7; 5.0]	0.764#	3.3 [1.6; 5.0]	2.2 [1.6; 3.7]	0.503#
Region primary	Head/Neck	8	2 (25)	6 (75)	0.660^	6 (75)	2 (25)	0.867^
	Trunk	25	9 (36)	16 (64)		20 (80)	5 (20)	
	Lower extremity	16	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)	
	Upper extremity	3	3 (18.8)	13 (81.3)		13 (81.3)	3 (18.8)	

TABLE 2 **Continued**

Characteristics		**N**	**S-100B<0.15 N=15**	**S-100B>0.15 N=37**	***p*-value**	**LDH<250 N=41**	**LDH>250 N=11**	***p*-value**
Melanoma type	Superficial spreading	28	9 (32.1)	19 (67.9)	1.000^	22 (78.6)	6 (21.4)	0.178^
	Nodulair	14	4 (28.6)	10 (71.4)		12 (85.7)	2 (14.3)	
	Other	1	0 (0)	1 (100)		0 (0)	1 (100)	
	Missing	9	2	7		7	2	
Ulceration	Yes	16	7 (43.8)	9 (56.3)	0.166^	13 (81.3)	3 (18.8)	0.717^
	No	24	5 (20.8)	19 (79.2)		18 (75)	6 (25)	
	Missing	12	3	9		10	2	
BRAF mutation	Yes	26	7 (26.9)	19 (73.1)	0.731^	23 (88.5)	3 (11.5)	**0.043**^
	No	21	4 (19)	17 (81)		13 (61.9)	8 (38.1)	
	Missing	5	4	1		5	0	

Data are displayed as n (%), median [interquartile range]
S-100B (µg/l), *LDH* Lactate dehydrogenase, (U/l)
^Fisher exact test
#Mann-Whitney U test
Values in **bold** are considered significant (p<0.05)

FIGURE 1 **Association between LDH and S-100B**

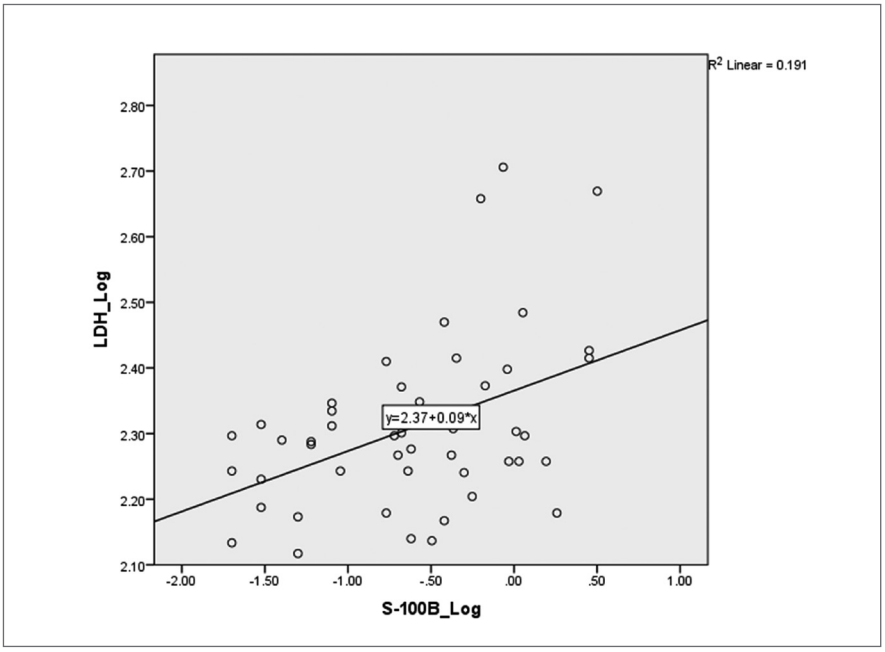


FIGURE 2 **Patient and tumor factors associated with high biomarker levels**

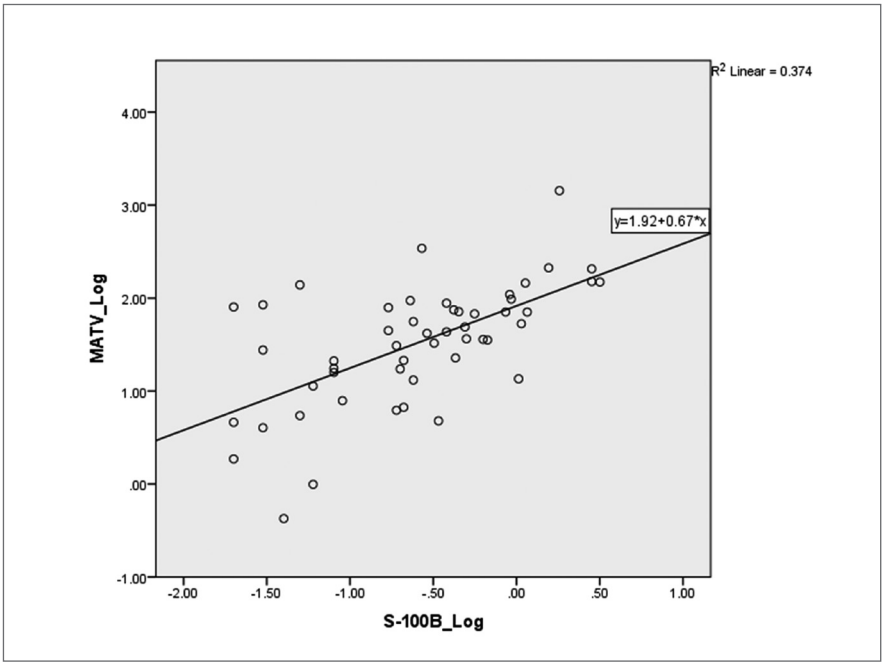


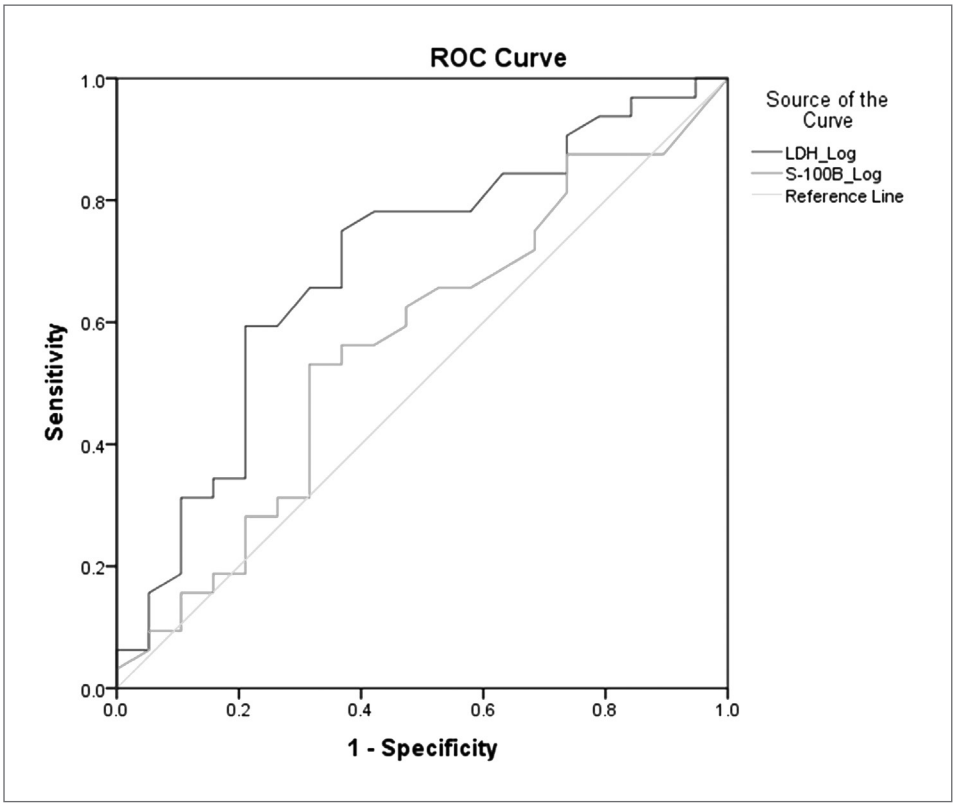
TABLE 3 **All correlations between PET derived metrics and biomarkers LDH and S-100B**

	LDH_Log	S-100B_Log	SUV_mean_LBM2_ Median_Log	MATV_Log	TLG_LBM2_ SUM_Log
LDH_Log	1	**0.437****	-0.023	0.160	0.139
S-100B_Log	**0.437****	1	0.140	**0.612****	**0.593****
SUV_Mean_LBM2_ Median_Log	-0.023	0.140	1	-0.043	0.238
MATV_Log	0.160	**0.612****	-0.043	1	**0.938****
TLG_LBM2_ Sum_Log	0.139	**0.593****	0.238	**0.938****	1

LDH lactate dehydrogenase; *SUV* Standard Uptake Value; *LBM2* Lean Body Mass; *MATV* Metabolic Active Tumor Volume; *Log* Log-transformed; *TLG* Total lesion Glycolysis

**Pearson correlation significant at the 0.01 level (2-tailed)

FIGURE 3 **ROC curve for dead of disease based on S-100B/LDH**



Recent studies have indicated that MATV and TLG are accurate prognostic markers for progression-free and recurrence-free survival in patients with cervical cancer and cutaneous melanoma.[36,37] In addition, MATV and TLG are stronger predictors of overall and melanoma-specific survival than SUV_{max}.[20,38] Kruijff et al. showed that, for clinically stage III melanoma patients, SUV_{mean} and S-100B were not correlated, but S-100B was a good predictor of disease-free survival. However, until now little has been known about the prognostic value of MATV and TLG and their relation to biomarkers in stage IV melanoma disease.[39,40]

For LDH, there seems to be a trend towards more elevated levels in elderly patients. This positive association between age and LDH in cancer has been noted previously, but the explanation is unclear.[41] It is well established that LDH has

important prognostic value in stage IV melanoma patients and it was, therefore, incorporated in the 7th Edition AJCC staging system in 2001.[42] We found 30-40% higher MATV and TLG values for the 11/52 patients with an elevated LDH (mean: 461U/l and median: 295U/l versus normal LDH with mean: 185U/l and median: 189U/l) which could partly account for the worse prognostic estimates. This is in line with the recent study of De Heer et al who showed that patients with elevated LDH have higher MATV and SUV values.[25] LDH levels may rise because of increasing tumor load in later stages of disease with more tumor necrosis, which might explain the poor prognosis and poor treatment responses. Because of their known poor response to systemic treatment, stage IV patients with a high LDH are often excluded from immune- and/or targeted treatment.[4]

In case of S-100B, it might be melanoma metabolically activity and proliferating tumor cells in advance of tumor necrosis that make the biomarker rise earlier.[25] In this study, S-100B was elevated in 37 patients (71%) and LDH in only 11 (21%) patients. This suggests that either S-100B is a more sensitive marker than LDH in the follow-up of melanoma patients or that they reflect different phases of disease progression.

TLG might be one of the better parameters to reflect actual tumor burden, as both FDG-uptake and tumor size are combined and when corrected for lean body mass it reflects 'real' tumor burden even more accurately.[20] In addition, in lung cancer, TLG is known to be an independent predictor of survival.[38] TLG was marginally associated with elevated S-100B levels, whereas LDH was not. However, in the present study, LDH was the only predictor of survival. This also suggests that LDH and S-100B reflect different stages of disease progression.

Future studies could focus on the role of S-100B and LDH in evaluating the biomarker response of stage IV melanoma patients receiving systemic therapy. Perhaps ^{18}F-FDG PET/CT scans could be substituted for biomarker measurements if further studies demonstrate persistent correlation between S-100B and/or LDH and tumor volume metrics over subsequent response evaluation scans during systemic treatment of stage IV patients. Only those with stage IV disease who are suitable for systemic therapy and have previously shown elevated S-100B biomarkers might be candidates for such biomarker response evaluation in the future.

FIGURE 4a **Kaplan Meier for LDH normal/elevated**

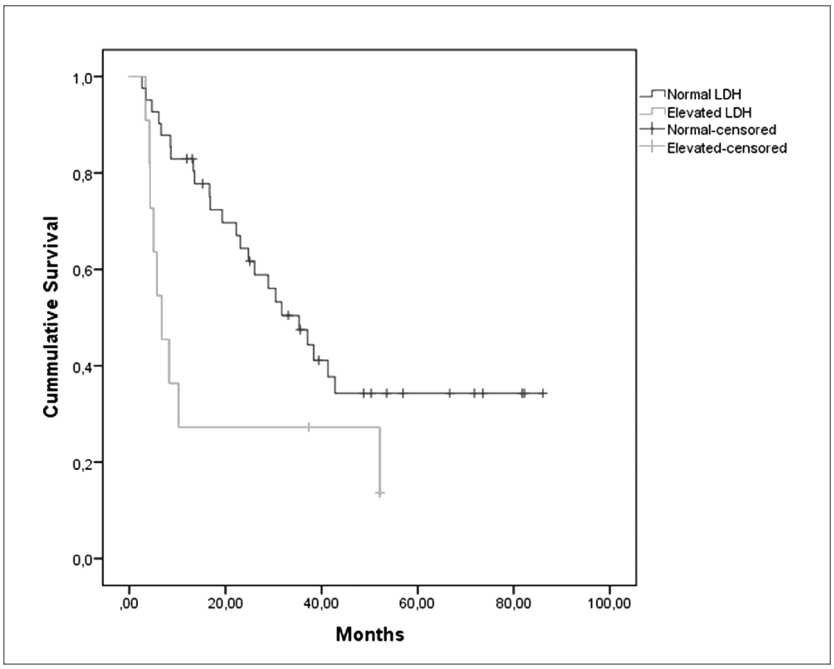
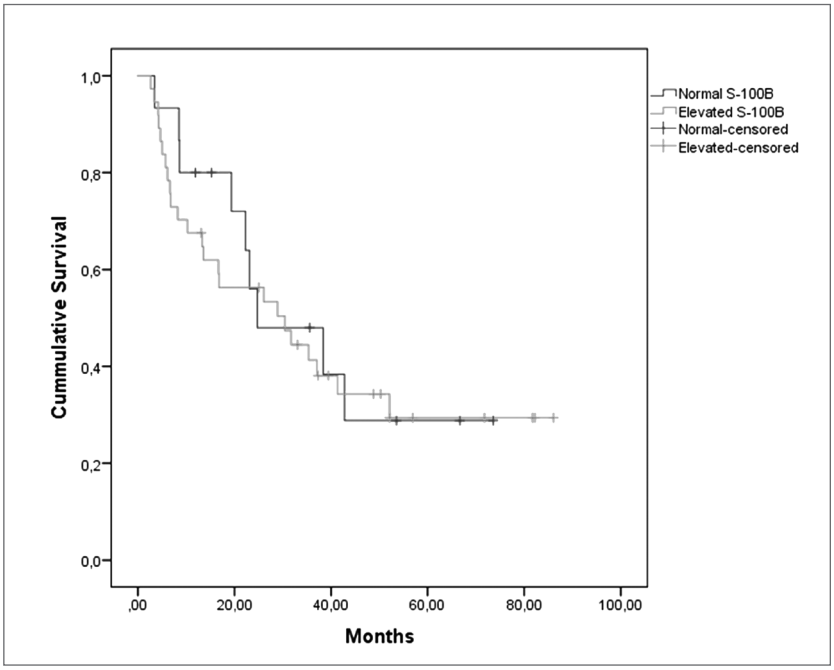


FIGURE 4b **Kaplan Meier for S-100B normal/elevated**



In order to effectively use S-100B in follow-up, it would be of great help to know which subgroup of patients will show elevation of their serum S-100B when there is melanoma recurrence. Unfortunately, the present study did not identify any patient or tumor characteristic that predicted a high sensitivity of S-100B in follow-up. This could be explained by the low sample size and the fact that this is a retrospective study. An option to identify suitable S-100B responders could be to evaluate the S-100B change after surgery with curative intent in patients with advanced stage III disease. Patients with S-100B elevation in association with metastatic melanoma and who have a decrease in S-100B after potentially curative surgery are designated as S-100B responders. These patients might be good candidates for follow-up with S-100B measurements to detect recurrent disease.

Reduction of follow-up and therapy evaluation scans will not only have a positive effect on healthcare costs, patient anxiety, and risk for second malignancies due to radiation, but will also decrease the risk of incidental findings and false positive scan results, which are found in a least half of asymptomatic stage III melanoma patients and even lead to unnecessary invasive procedures.[43]

Conclusion

The associations between the biomarkers S-100B and LDH in the serum and tumor load, as assessed by MATV/TLG on ^{18}F-FDG PET/CT scans, suggests that S-100B is correlated with disease progression (higher tumor burden) in contrast to LDH. However, LDH has a predictive value for survival in contrast to S-100B. Both LDH and S-100B seem to describe different aspects of the metastatic disease, tumor proliferation and tumor necrosis. Future research should focus on the possibility of using S-100B and LDH monitoring in appropriate patients with resected stage III disease as a useful alternative to routine follow-up with ^{18}F-FDG PET/CT scans.

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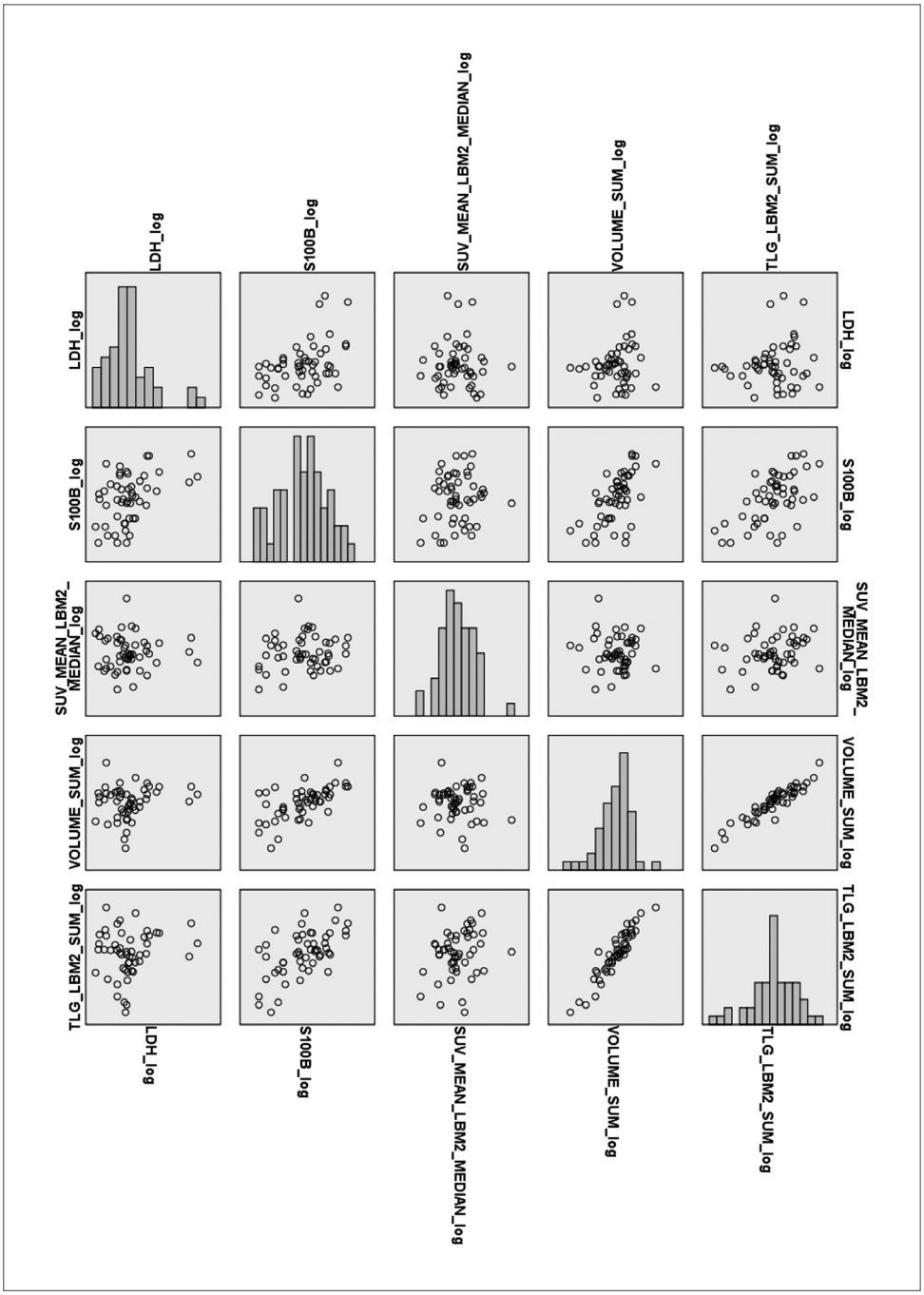
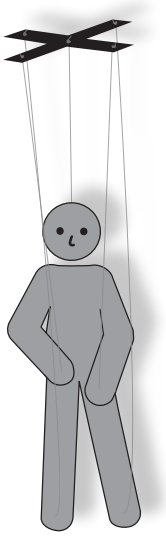
APPENDIX A **All correlations between PET derived metrics and biomarkers LDH and S-100B**

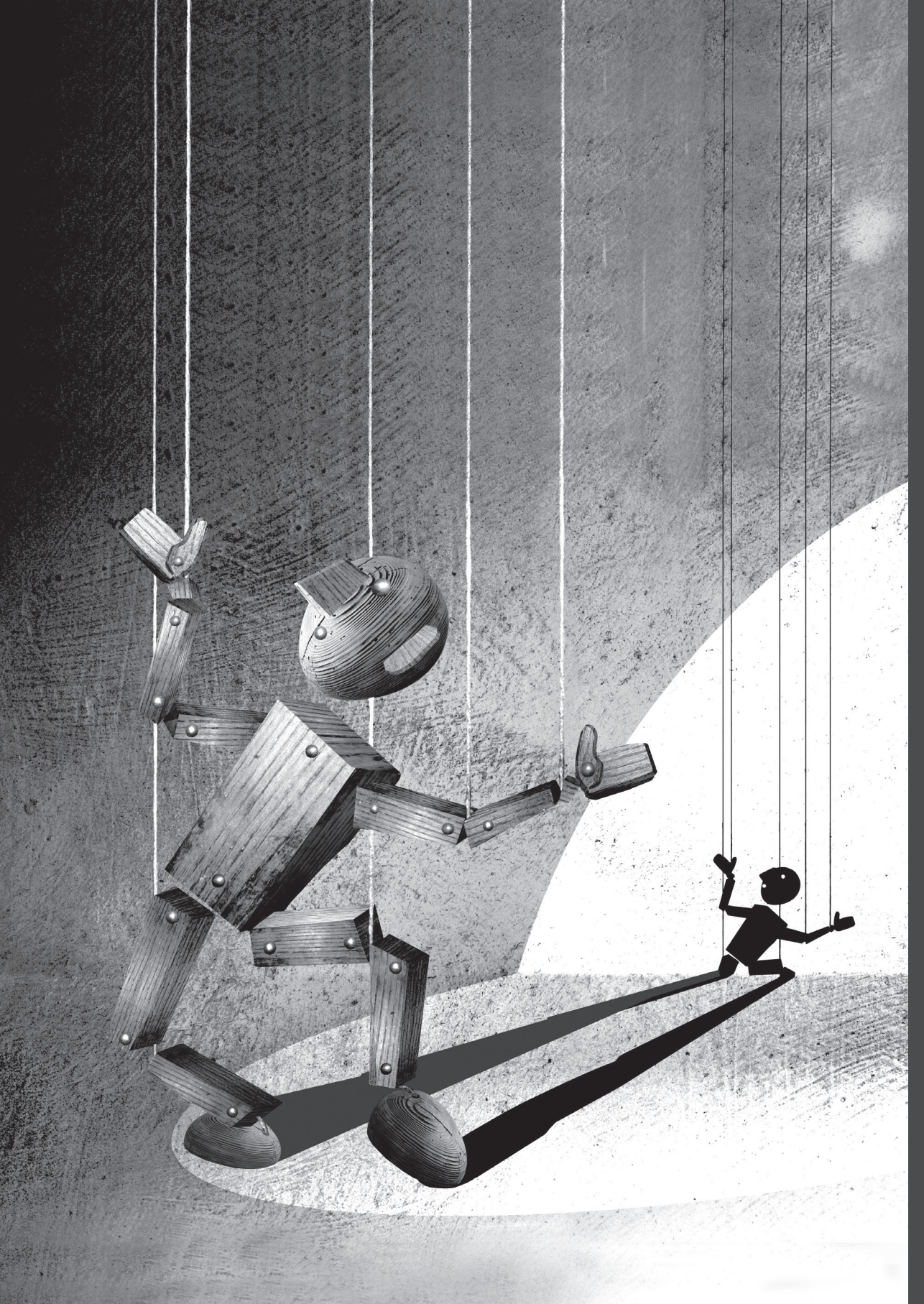


APPENDIX B ^{18}F-FDG PET/CT derived metrics on a per-patient basis, stratified by S-100B (S-100B normal/S-100B elevated) or LDH (LDH normal/LDH elevated)

	S-100B<0.15 n=15	S-100B>0.15 n=37	*p*-value	LDH<250 n=41	LDH>250 n=11	*p*-value
SUV_{peak}						
Maximum	0.63 ± 0.08	0.94 ± 0.05	**0.001**	0.84 ± 0.05	0.91 ± 0.05	0.319
Median	0.33 ± 0.09	0.48 ± 0.05	0.126	0.43 ± 0.05	0.46 ± 0.08	0.776
SUV_{mean}						
Maximum	0.55 ± 0.06	0.80 ± 0.04	**0.002**	0.73 ± 0.05	0.75 ± 0.19	0.823
Median	0.35 ± 0.07	0.47 ± 0.04	0.143	0.44 ± 0.04	0.43 ± 0.05	0.951
SUV_{max}						
Maximum	0.74 ± 0.08	1.07 ± 0.04	**<0.001**	0.96 ± 0.05	1.05 ± 0.06	0.418
Median	0.67 ± 0.08	0.83 ± 0.05	0.08	0.78 ± 0.05	0.79 ± 0.07	0.896
Total MATV	1.00 ± 0.18	1.74 ± 0.08	**<0.001**	1.40 ± 0.10	2.00 ± 0.07	**<0.001**
Total TLG	1.47 ± 0.20	2.40 ± 0.09	**<0.001**	2.00 ± 0.12	2.62 ± 0.10	**<0.001**
Number of lesions	4 (1-27)	10 (1-66)	**0.027**[#]	7 (1-55)	9 (1-66)	0.363[#]

Data are displayed as mean ± SEM
T-tests are used to calculate significance
[#]Mann-Whitney U test
PET derived metrics are corrected for Lean Body Mass and Log-transformed
MATV (ml), *S-100B* (µg/l), *LDH* Lactate dehydrogenase (U/l), ^{18}F-FDG PET-CT fluorine-18-Fluorodeoxyglucose positron emission tomography with computed tomography, SUV_{peak} peak standardized uptake value, SUV_{mean} mean standardized uptake value, SUV_{max} maximum standardized uptake value, *MATV* metabolically active tumor volume, *TLG* total lesion glycolysis
Maximum $SUV_{peak/mean/max}$ highest value of a lesion out of all metastatic lesions.
Median $SUV_{peak/mean/max}$ median value of a lesion out of all metastatic lesions.
Values in **bold** are considered significant (p<0.05)





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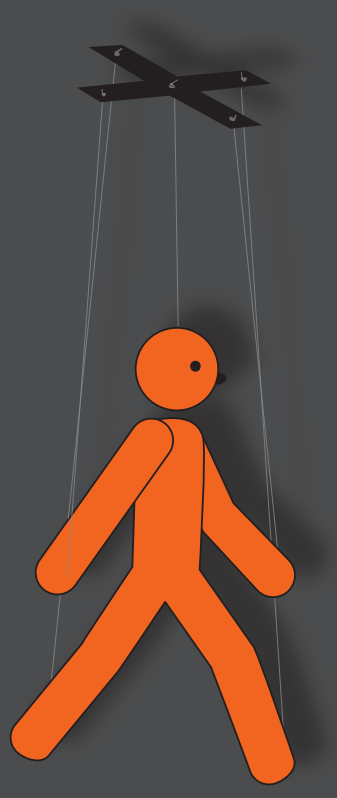
Summary and conclusion



Skin cancer is the most common type of cancer in the Netherlands. The increase in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) is mainly due to the increased life expectancy of the Dutch population. The prognosis of the BCC and SCC is generally good with a relative 5-year survival rate of 95%. For Melanoma, another type of skin cancer, survival depends on the stage of disease, with 92% 5-year survival for all stages combined. This number is quite high because more than 50% of the melanomas are thin melanomas (Breslow <1mm). However, mortality is 4.6 per 100,000 adults. The incidence of BCC, SCC and melanoma has been increasing for decades, but the incidence of the melanoma now appears to be stabilizing for the first time. At the same time, melanoma is diagnosed more often at an early stage, with a high cure rate after surgical resection. In 2018, the 3-year survival rate of stage I melanoma in the Netherlands was 100%, stage II 84%, stage III melanoma 69% and stage IV 17%.[1] Early diagnosis and improved melanoma treatment continue to increase the prevalence of melanoma.

Due to the new available systemic (adjuvant) treatment options in melanoma patients with targeted and/or immunotherapy, the 5-year and 10-year survival of advanced melanoma will probably improve in the next years. Because an increasingly amount of patients with a melanoma will be diagnosed and the treatment options are improving, more patients will be in follow-up for their melanoma. Besides, patients have to be properly educated about self-detection of recurrences. Earlier detection of recurrent disease offers the possibility to start systemic treatment in earlier phase. An additional advantage is that the systemic treatments with targeted and/or immunotherapy is more effective in patients with low-volume disease.

In view of the increasing prevalence of the melanoma there is a need for, on the one hand, reducing outpatient clinics for stage I-II melanoma, and on the other hand minimally invasive detection of regional metastasis for stage IB-II melanoma. Furthermore, early, cost-effective detection of recurrences after treatment of regionally metastatic melanoma, stage III will be increasingly important.

This thesis focuses on various aspects of the multidisciplinary treatment of melanoma. The value of staging in the treatment of localized melanoma using the sentinel lymph node biopsy (SLNB) and advanced melanoma with the biomarkers S-100B and LDH and fluorine-18-deoxyglucose Positron Emission Tomography/ Computer Tomography (^{18}F-FDG PET/CT). Besides, decreasing the number of outpatient clinics in stage IB-II melanoma will be discussed.

The prognosis of clinical stage I-II melanoma patients is based on different clinical and pathological factors such as primary tumor site, Breslow thickness, mitotic rate, ulceration, regression, histopathological subtype of melanoma, status of sentinel lymph node (SLN), age and gender. Currently, the main predictor of the outcome for patients with localized melanoma is the presence of regional lymph node metastases. Can SLNB negative patients suffice with a less intensive short- and long-term follow-up? But are all eligible melanoma patients, stage IB-II, offered a SLNB in the Netherlands? Do socio-economic factors influence whether or not a SLNB is performed?

About 40% of the American population is obese (BMI >30). The number of obese Dutch people has continued to increase in recent decades and amounts in 2018 15%. Obesity is developing slowly and is a serious health problem associated with various diseases such as diabetes, cardiovascular morbidity, disorders of the musculoskeletal system, but is also (jointly) responsible for the development of at least 13 different types of cancer. Recent research suggested that obesity might be associated with improved progression free - and overall survival in male metastatic melanoma patients treated with targeted and/or immune therapy. What effects does obesity have on the prognosis of localized melanoma? A better or a worse prognosis?

During the last two decades, extensive research has been performed into the value and application possibilities of ^{18}F-FDG PET/CT and biomarker staging with S-100B and LDH. Technological developments now make it possible to quantitatively measure tumor load in metastatic melanoma with ^{18}F-FDG PET/CT scans. Tumor load is of prognostic significance, as is the value of the biomarkers S-100B and LDH. Is there a relationship between 'tumor load' determined with ^{18}F-FDG PET/CT scans and the biomarkers S-100B and LDH? And if so, what is the prognostic value? What does this knowledge mean for the follow-up of regional metastasized melanoma?

The introduction to this thesis provides a global overview of the current melanoma incidence, prevalence, staging, follow-up, biomarkers, treatment, prognosis and healthcare costs. **Chapters II-VI** provide an answer to the five questions formulated in the introduction. **Chapters VII and VIII** provide an English, respectively Dutch summary and conclusion of the findings of this thesis. Future perspectives, **chapter IX**, looks in more detail at future melanoma research.

Follow-up stage IB-II

The first results of the multicenter and randomized clinical trial on the value of follow-up in patients with stage IB-II melanoma, the MELFO study, which compared the follow-up schedule of the melanoma guideline of the Dutch Melanoma Working Group with a less frequent follow-up schedule. The results after one-year follow-up, published in 2016, showed no difference in the number of recurrences and the well-being of patients. In addition, the reduced follow-up scheme provided an economic benefit. The 3-year results of the MELFO study are described in **chapter II**. Two thirds of the recurrences were by the patients themselves, in accordance with a percentage we had previously found in the Netherlands and Australia. The recurrence rate was 13.9% after 3 years. After three years, 7.2% of the patients died as a result of the melanoma. There were no differences in recurrence-free survival and melanoma-specific survival. There was no difference in the well-being of patients in both groups. The cost reduction was considerable and amounted to 39% after 3 years. A stage-based follow-up of stage IB-II is justified and accompanied by significant cost savings. We now have to wait for new biomarkers that are able to reliable predict survival for stage I-II melanoma patients.[2]

Implementation of sentinel lymph node biopsy in the Netherlands

The sentinel lymph node biopsy (SLNB) procedure was simultaneously introduced in the Netherlands in 1994 by the Department of Surgical Oncology of the UMCG and AVL. In 2010, the 7th edition of the AJCC staging was introduced, which meant that melanoma clinical stage IB-II melanoma patients were eligible to undergo a minimally invasive staging procedure of the regional lymph node bearing area using a SLNB. In 2013, the SLNB was performed in less than 50% of all eligible patients in the Netherlands, with a large difference between the eight regions of the Comprehensive Cancer Centers. With the data from the Dutch Cancer Registry, the implementation of the SLNB after the introduction of the 7th edition of the AJCC staging manual, was re-examined in the Netherlands. The results are described in **chapter III**. During the period 2010-2016, the number of performed SLNBs increased from 40% to 65%. The SLNB procedure was significantly more often performed in the North-East region 74% ($p<0.01$). Multivariate analysis showed that the SLNB procedure was performed less often in women, elderly people and patients with melanoma in the head- and neck region. Socio-economic status did not, as in the past, affect the implementation of a SLNB. With the advent of effective targeted and/or immunotherapy therapy, which appears

to be more effective in patients with low 'tumor load', a further implementation of the SLNB within multidisciplinary melanoma treatment in the Netherlands seems necessary. A percentage of 80%, similar as the SLNB percentage in breast cancer, seems realistic.

Obesity

Chapter IV provides an answer to the question whether in the Netherlands obesity (BMI>30) is of prognostic value in patients with localized melanoma. A study was conducted in patients with a clinical stage IB-II melanoma who were treated in the UMCG during the period 1995-2018. All patients underwent the same treatment protocol with regard to staging, sentinel lymph node biopsies (SLNB) and excision of the melanoma with a margin of 1 or 2 cm based on its Breslow thickness. With a positive SLNB, a completion lymph node dissection (CLND) was performed or patients were followed with a routinely ultrasound of the lymph node bearing area. The latter was performed within the MSLT II study. Obesity had no significant influence on recurrence-free period, on melanoma-specific survival and overall survival. Elderly melanoma patients, arm location, increased Breslow thickness, presence of ulceration, increased mitotic rate and a positive SLNB were significantly associated with a reduced relapse-free period, melanoma-specific survival and overall survival. In contrast, histology, gender and socio-economic status (SES) were not associated. The hypothesis that obesity is associated with a poorer disease-free and overall survival could not be confirmed in this study. There was a noticeable trend that obese melanoma patients seemed to have a worse prognosis. It is therefore advisable to repeat this study over a number of years, in a larger (multicenter) cohort. The groups should be comparable for relevant melanoma and patient-related characteristics, and preferably, if possible, should smoking be included as a prognostic factor.

Follow-up stage III

The purpose of follow-up is preferably a cost-effective detection of a loco-regional recurrence or distant metastases at in early phase in the hope that surgical and/or systemic and/or radiotherapeutic treatment of the recurrence can contribute to an improvement in the disease-free and/or overall survival or assisting in an effective palliative treatment.

The majority of recurrences in stage I-II melanoma are local and/or regional, sporadically distantly. Approximately 70% of these recurrences are detected by

the patient themselves. The majority of recurrences in curative treated stage III melanoma patients are distant metastasis. S-100B is a sensitive biomarker in the diagnosis, therapy evaluation and follow-up of the melanoma patients. PET with ^{18}F-FDG PET/CT in the follow-up of stage III melanoma can detect early, asymptomatic recurrences. The costs of such a PET follow-up schedule are considerable, but what will it ultimately yield? Recently, the Melanoma Institute of Australia reported that false positive results with PET/CT were found in no less than 50% of these stage III melanoma patients for whom additional diagnostic work-up was indicated.[3] Therefore, PET/CT in the follow-up of curative stage III melanoma treatment in the Netherlands is currently not included in follow-up programs, with the exception of some clinical trials with systemic adjuvant treatment. **Chapter V** describes a study in which the value of the biomarker S-100B as an indicator for performing a ^{18}F-FDG PET/CT scan in the follow-up of stage III melanoma (7th edition AJCC staging) is investigated. In this study, 30 patients (71%) developed a symptomatic or asymptomatic recurrence. Seven of the recurrences were detected early with the aid of the S-100B biomarker, being 10% of all asymptomatic patients in follow-up and 23% of all patients with a recurrence. Although the biomarker S-100B used in the regular follow-up of stage III melanoma cannot rule out a recurrence, it can be a cost-effective indicator for performing an ^{18}F-FDG PET/CT scan if the biomarker S-100B is increased.

Tumor load and tumor markers

It has recently been possible to calculate on metastases using ^{18}F-FDG PET/CT scan (i.e. Standard Uptake Value ($SUV_{mean/max}$), Metabolic Active Tumor Volume (MATV) and Total Lesion Glycolysis (TLG=SUV_{mean}xMATV)). Previous research has already shown the relationship between SUV_{max} and S-100B in stage III melanoma. The relationship between the biomarkers S-100B and LDH and MATV and TLG was investigated in melanoma stage IV and described in **chapter VI**. The study showed that there was a marginal correlation between S-100B and LDH and MATV and TLG measured with ^{18}F-FDG PET/CT. In addition, it was found that S-100B was increased more often than LDH in stage IV melanoma (71% vs. 21%). S-100B therefore appears to be already elevated with a lower 'tumor load' compared to LDH, but LDH is the strongest predictor in terms of survival.

Conclusion

A further implementation of the SLNB procedure in the Netherlands up to 80% seems realistic. Due to the better staging of stage I-II melanoma with the SLNB, in patients with a pathological stage IB-II can a less intensive outpatient clinic be performed without an increased risk of recurrence, the same quality of life, but with a significant cost reduction. In view of the worldwide increasing obesity rate, also among melanoma patients, and the trend towards a worse disease-free survival in obese clinical stage IB-II melanoma patients, an additional multicenter study is desirable in the near future, whereby smoking behavior must be included as a potential risk factor. Finally, additional research into the value in follow-up with the biomarkers S-100B and LDH in curatively treated stage III melanoma patients is indicated. Are both biomarkers indeed good indicators to perform a ^{18}F-FDG PET/CT for staging the presence or absence of distant metastasis in the follow-up of stage III melanoma.

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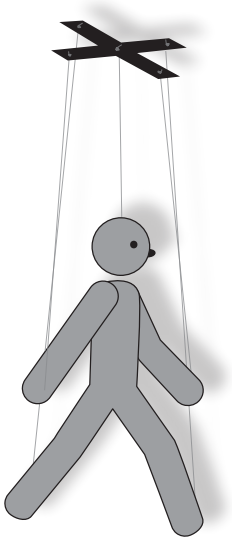

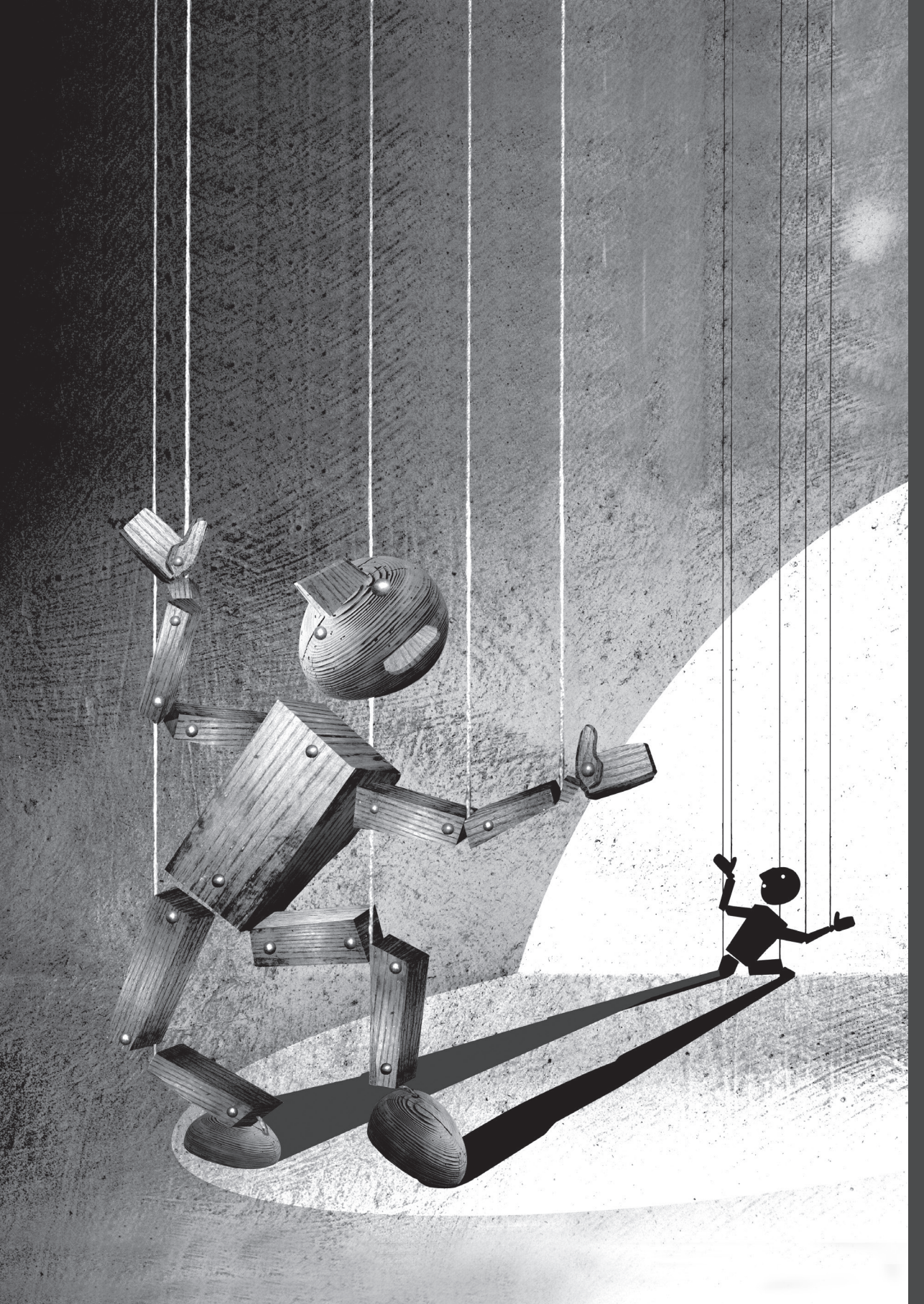

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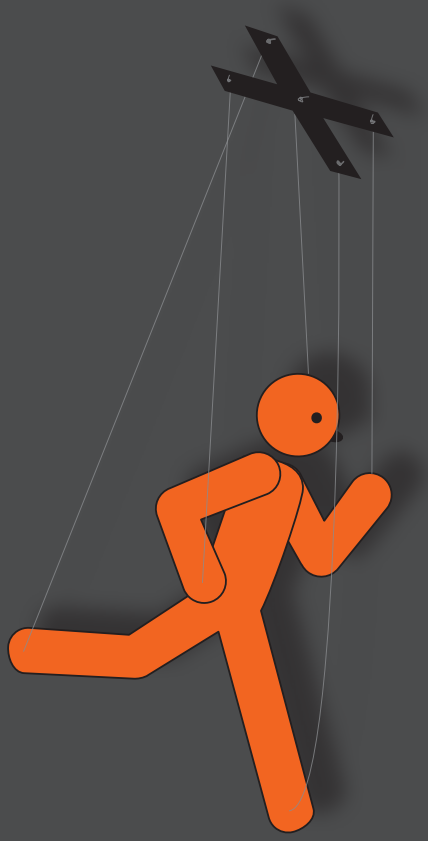
Samenvatting en conclusie



Introductie

Huidkanker is de meest voorkomende kankersoort in Nederland. De toename van het basaalcelcarcinoom (BCC) en het plaveiselcelcarcinoom (PCC) is grotendeels toe te schrijven aan de vergrijzing van de Nederlandse bevolking. De prognose van het BCC en PCC is over het algemeen goed met een relatieve 5-jaarsoverleving van 95%. Bij een andere belangrijke vorm van huidkanker, namelijk het melanoom, is de overleving afhankelijk van het stadium waarin de ziekte zich bevindt. Voor alle stadia samen ligt de 5-jaars overleving weliswaar rond de 92%. Dit komt omdat meer dan vijftig procent van de melanomen een Breslow dikte heeft van <1 mm. De melanoomsterfte bedraagt echter 4,6 per 100.000 volwassenen. De incidentie van het BCC, PCC en melanoom neemt al decennia toe, maar de incidentie van het melanoom lijkt zich nu voor het eerst te stabiliseren. Daarnaast wordt de diagnose melanoom vaker in een vroeg stadium gesteld, met daarbij een zeer grote kans op genezing na chirurgische behandeling. In 2018 bedroeg in Nederland de 3-jaars overleving van stadium I melanoom 100%, stadium II 84%, stadium III melanoom 69% en stadium IV 17%.[1] Door de vroegtijdige diagnostiek en de verbeterde melanoombehandeling neemt de prevalentie van melanoom steeds verder toe.
Door de nieuwe beschikbare systemische (adjuvante) behandelmogelijkheden met doelgerichte- en/of immunotherapie, is de verwachting dat de komende jaren de 5- en 10-jaars overleving van de hogere stadia van het melanoom zullen verbeteren. Omdat er steeds meer patiënten met een melanoom worden gediagnosticeerd en er steeds meer en betere behandelingsmogelijkheden beschikbaar komen, zullen er meer patiënten poliklinisch gecontroleerd moeten gaan worden. Daarnaast moeten patiënten goed geïnstrueerd worden hoe eventuele recidieven door zelf-onderzoek kunnen worden vastgesteld. Het eerder vaststellen van een recidief biedt de mogelijkheid eerder te starten met (adjuvante) systemische behandeling. Het bijkomende voordeel is dat de systemische behandelingen met doelgerichte- en/of immunotherapie effectiever werken bij geringe 'tumor load'.
Er is dus, gezien de toenemende prevalentie van het melanoom, behoefte aan enerzijds het reduceren van poliklinische controles bij stadium I-II melanoom en anderzijds een toenemende behoefte aan het minimaal invasief detecteren van regionale metastasering bij stadium IB-II melanoom. Tenslotte is er behoefte aan het vroegtijdig, kosteneffectief detecteren van recidieven na behandeling van het regionaal gemetastaseerd melanoom, stadium III.

Dit proefschrift richt zich op verschillende aspecten van de multidisciplinaire behandeling van het melanoom. De waarde van de stadiëring bij de behandeling van het gelokaliseerde melanoom middels de schildwachtklierbiopsie (SWK) en de hogere stadia van het melanoom met behulp van de biomerkstoffen S-100B en LDH en Positron Emissie Tomografie/Computer Tomografie (PET/CT). Tevens is er aandacht voor het reduceren van poliklinische follow-up bezoeken bij stadium IB-II melanoom .

De prognose van klinische stadium I-II melanoompatiënten is gebaseerd op verschillende klinische- en pathologische factoren zoals primaire tumorplaats, Breslow-dikte, mitotische delingen, ulceratie, regressie, histopathologisch subtype van het melanoom, status van de schildwachtklier (SWK), leeftijd en geslacht. Momenteel is de belangrijkste voorspeller van de uitkomst voor patiënten met gelokaliseerd melanoom de aanwezigheid van regionale lymfeklier metastasen. Betekent dit dat voor de SWK-negatieve patiënten misschien volstaan kan worden met een minder intensieve korte- en lange termijn follow-up? Maar krijgen wel alle daarvoor in aanmerking komende melanoompatiënten, stadium IB-II, in Nederland een SWK aangeboden? Zijn sociaaleconomische factoren van invloed bij het wel of niet uitvoeren van een SWK-biopsie in Nederland?

Ongeveer 40% van de Amerikaanse bevolking is obees (BMI >30). Het aantal obese Nederlanders neemt de laatste decennia steeds verder toe en bedroeg in 2018 15%. Obesitas komt in toenemende mate voor en is een serieus maatschappelijk probleem dat gepaard gaat met diverse ziektes zoals diabetes, cardiovasculaire morbiditeit, aandoeningen van het steun en bewegingsapparaat, en is ook (mede) verantwoordelijk voor de ontwikkeling van zeker 13 verschillende soorten kanker. Recent onderzoek suggereerde dat de prognose van ver-voortgeschreden melanoompatiënten behandeld met doelgerichte- en/of immunotherapie gunstiger was bij obese, mannelijke melanoompatiënten. Welke effecten heeft obesitas bij het gelokaliseerde melanoom? Een betere of een slechtere prognose?

De laatste twee decennia is veel onderzoek gedaan naar de waarde en de toepassingsmogelijkheden van FDG PET/CT scans en stadiëring met behulp van de biomerkstoffen S-100B en LDH. De technologische ontwikkelingen maken het nu mogelijk om met FDG PET/CT scans de 'tumor load' bij het gemetastaseerde melanoom kwantitatief te meten. Tumor load is van prognostische waarde, evenals de waarde van de biomerkstoffen S-100B en LDH. Is er een relatie tussen de met behulp van FDG PET/CT scans vastgestelde 'tumor load' en de biomerkstoffen

S-100B en LDH? En zo ja, wat is dan daarvan de prognostische waarde? Wat betekent deze kennis voor de follow-up van het gemetastaseerd melanoom?
De inleiding van dit proefschrift geeft een globaal overzicht van de huidige incidentie, prevalentie, stadiering, follow-up, biomerkstoffen, behandeling, prognose en zorgkosten in Nederland van het melanoom. In de **hoofdstukken II-VI** wordt een antwoord gegeven op de in de inleiding geformuleerde vraagstellingen. De **hoofdstukken VII en VIII** geven een, Engelse, respectievelijke Nederlandse samenvatting en conclusie van de bevindingen van het onderzoek. In 'Future perspectives', **hoofdstuk IX**, wordt nader ingegaan op het toekomstige melanoom onderzoek.

Follow-up stadium IB-II

De eerste resultaten van de multicentrische en gerandomiseerde klinische studie naar de waarde van de follow-up bij patiënten met een stadium IB-II melanoom, de MELFO studie, waarin het follow-up schema van de richtlijn van de Nederlandse Melanoom Werkgroep vergeleken werd met een minder intensief follow-up schema lieten in 2016 geen verschil zien in het aantal recidieven en het welzijn van de patiënten na 1 jaar. Daarnaast leverde het verkorte schema een economisch voordeel op. De 3-jaars resultaten van deze MELFO studie zijn beschreven in **hoofdstuk II**. Tweederde van de recidieven werd door de patiënten zelf vastgesteld, overeenkomstig met een eerder door ons gevonden percentage in Nederland en Australië. Het recidiefpercentage bedroeg na 3 jaar 13.9%. Na drie jaar waren 7.2% van de patiënten overleden ten gevolge van het melanoom. Er waren geen verschillen in de recidiefvrije overleving en melanoomspecifieke overleving. Er was geen verschil in het welbevinden van de patiënten in beide groepen. De kostenreductie was aanzienlijk en bedroeg na 3 jaar 39%. Daarmee is aangetoond dat een op het stadium gebaseerde follow-up van stadium IB-II gerechtvaardigd en verantwoord is en gepaard gaat met een aanzienlijke kostenbesparing. Het wachten is nu op nieuwe biomarkers die in staat zijn de prognose van stadium I-II betrouwbaar te voorspellen.[2]

Implementatie schildwachtklierbiopsie in Nederland

De schildwachtklier (SWK) biopsie procedure werd in Nederland door het UMCG en AVL gelijktijdig in 1994 geïntroduceerd. In 2010 werd de 7^{e} editie van de AJCC stadiëring ingevoerd en dat betekende voor het melanoom dat klinische stadium IB-II melanoompatiënten in aanmerking kwamen voor het uitvoeren van een

minimaal invasieve stadiërende ingreep van het regionale klierstation met behulp van een SWK-biopsie. In 2013 werd de SWK bij minder dan 50% van de daarvoor in aanmerking komende patiënten in Nederland uitgevoerd, waarbij er een groot verschil was tussen de acht regio's van de Integrale Kanker Centra (IKCs). Met behulp van data van de Nederlandse Kankerregistratie werd de implementatie van de SWK na de invoering van de 7e editie van de AJCC stadiëring in Nederland opnieuw onderzocht. De resultaten worden beschreven in **hoofdstuk III**. Gedurende de periode 2010-2016 steeg het aantal uitgevoerde SWK's van 40% tot 65%, waarbij de SWK procedure significant vaker in de IKC regio Noord-Oost werd uitgevoerd 74% ($p<0.01$). Multivariate analyse liet zien dat de SWK minder werd uitgevoerd bij vrouwen, oudere mensen en patiënten met een melanoom in het hoofd-hals gebied. Sociaaleconomische status is niet langer van invloed op het uitvoeren van een SWK, zoals in het verleden wel aangetoond was. Met de komst van de effectieve doelgerichte- en/of immunotherapie therapie, die met name effectiever lijkt te zijn bij een geringe 'tumor load', lijkt een verder implementatie van de SWK binnen de multidisciplinaire melanoom behandeling in Nederland noodzakelijk. Een percentage van 80%, overeenkomstig met die van het mammacarcinoom lijkt reëel.

Obesitas

In **hoofstuk IV** wordt een antwoord gegeven op de vraag of in Nederland obesitas (BMI>30) bij patiënten met een initieel gelokaliseerd melanoom van prognostische betekenis is. Hiertoe werd een onderzoek uitgevoerd in patiënten met een klinisch stadium IB-II melanoom die gedurende de periode 1995-2018 in het UMCG werden behandeld. Alle patiënten ondergingen hetzelfde behandelprotocol met betrekking tot de stadiëring door middels van een SWK-biopsie. De (re-) excisie marges van het melanoom, 1 of 2 cm, waren gebaseerd op de Brewlow dikte van het melanoom. Bij een positieve SWK werd een complementerende klierdissectie verricht of werden patiënten gecontroleerd met een echografie van het betreffende klierstation. Dit laatste geschiedde binnen de MSLT II studie. Obesitas had geen significante invloed op de recidiefvrije periode, op de melanoom-specifieke en algehele overleving. Oudere leeftijd, armlocatie, toegenomen Breslow-dikte, aanwezigheid van ulceratie, verhoogde mitose activiteit en een positieve SWK waren significant geassocieerd met verminderde recidiefvrije periode, melanoom-specifieke en algehele overleving. Daarentegen waren histologie, geslacht en sociaaleconomische status (SES) niet geassocieerd. De veronderstelde hypothese dat obesitas gepaard gaat met een slechtere ziektevrije- en algehele overleving kon in dit onderzoek dus niet worden

bevestigd. Wel was er een trend waarneembaar dat obese melanoom patiënten een slechtere prognose leken te hebben. Het is derhalve aan te bevelen deze studie over een aantal jaren, in een groter (multicenter) cohort, te herhalen. De groepen dienen wel vergelijkbaar te zijn voor relevante melanoom- en patiënt gerelateerde karakteristieken, en bij voorkeur ook, indien mogelijk, moet de invloed van roken als prognostische factor worden meegenomen.

Follow-up stadium III

Het doel van follow-up is bij voorkeur het kosteneffectief detecteren van een loco-regionaal recidief of afstandsmetastasen in een vroegtijdig stadium. De hoop is dat een tijdige chirurgische en/of systemische en/of radiotherapeutische behandeling van het recidief kan bijdragen aan een verbetering van de ziektevrije- en/of algehele overleving of een effectieve palliatieve behandeling.
Het merendeel van de recidieven bij stadium I-II melanoom is lokaal en/of regionaal en slechts sporadisch is er sprake van een metastase op afstand. Ongeveer 70% van de loco-regionale recidieven wordt door de patiënt zelf gedetecteerd. Bij de in opzet curatief behandelde melanoompatiënten stadium III, is er bij het merendeel van de patiënten bij recidivering sprake van metastasering op afstand. S-100B is een gevoelige biomerkstof bij de diagnostiek, therapie-evaluatie en follow-up van het melanoom. Positron Emissie Tomografie/Computed Tomography (PET/CT) met ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) in de follow-up van stadium III melanoom kan vroegtijdig, asymptomatische recidieven vaststellen. De kosten van een dergelijke ^{18}F-FDG PET/CT scan follow-up zijn aanzienlijk, maar wat levert het uiteindelijk op? Recentelijk werd door het Melanoma Institute of Australia gerapporteerd dat bij maar liefst 50% van deze stadium III patiënten valspositieve uitslagen werden gevonden, waarvoor weer aanvullende diagnostiek was geÏndiceerd.[3] Derhalve zal in Nederland een ^{18}F-FDG PET/CT scan, na curatieve behandeling van stadium III, voorlopig geen onderdeel uitmaken van follow-up programma's, met uitzondering van klinische trials met systemische adjuvante behandeling. In **hoofdstuk V** wordt een onderzoek beschreven waarbij de waarde van de biomerkstof S-100B als een indicator voor het verrichten van een ^{18}F-FDG PET/CT scan in de follow-up van stadium III melanoom (7^{e} editie AJCC stadiëring) wordt onderzocht. In dit onderzoek ontwikkelden 30 patiënten (71%) een symptomatische of asymptomatisch recidief. Zeven van de recidieven werden vroegtijdig vastgesteld met behulp van de biomerkstof S-100B, zijnde 10% van alle in follow-up zijnde asymptomptomatische patiënten en 23% van alle patiënten

met een recidief. Hoewel de biomerkstof S-100B gebruikt in de reguliere follow-up van stadium III melanoom een recidief niet kan uitsluiten, kan het wel een kosteneffectieve indicator zijn voor het verrichten van een ^{18}F-FDG PET/CT scan in het geval de biomerkstof S-100B verhoogd is.

Tumor load en tumormerkstoffen

Het is sinds kort mogelijk om met behulp van ^{18}F-FDG PET/CT scan aan alle melanoommetastasen metingen te verrichten. Voorbeelden hiervan zijn de Standaard Uptake Value ($SUV_{mean/max}$), metabolic active tumorvolume (MATV) en Total Lesion Glycolysis (TLG) (SUV_{mean}xMATV). Eerder onderzoek heeft reeds de relatie tussen SUV_{max} en S-100B bij melanoom stadium III aangetoond. De relatie tussen de biomerkstoffen S-100B en LDH en MATV en TLG werd onderzocht bij melanoom stadium IV en beschreven in **hoofdstuk VI**. Het onderzoek liet zien dat er mogelijk een marginale correlatie is tussen S-100B en LDH en MATV en TLG, gemeten met ^{18}F-FDG PET/CT scan. Daarnaast bleek dat S-100B vaker verhoogd was dan LDH bij stadium IV melanoom (71% vs. 21%). S-100B lijkt verhoogd te zijn bij reeds een lagere hoeveelheid MATV, dan LDH. LDH laat echter zien de sterkste voorspeller te zijn wat betreft de overleving.

Conclusie

Een verdere implementatie van de SKW-procedure in Nederland tot 80% lijkt realistisch. Door de betere stadiëring van stadium I-II melanoom met de SWK, kan bij patiënten met een pathologisch stadium IB-II een verantwoorde, minder intensieve poliklinische controles worden uitgevoerd zonder dat dit gepaard gaat met verhoogde kans op recidief bij een gelijkblijvende kwaliteit van leven, maar wel met een aanzienlijke kostenreductie. Gezien de wereldwijde toename van obesitas, ook onder melanoompatiënten, en de trend tot een slechtere ziektevrije overleving bij obese klinisch stadium IB-II melanoompatiënten is aanvullend multicenter onderzoek gewenst, waarbij ook het rookgedrag als risicofactor moet worden meegenomen. Tenslotte is aanvullend onderzoek geïndiceerd naar de waarde van S-100B en LDH in de follow-up van in opzet curatief behandelde stadium III melanoompatiënten. Zijn beide biomerkstoffen inderdaad goede indicatoren voor het uitvoeren van een ^{18}F-FDG PET/CT scan ter stadiëring van de aan- of afwezigheid van metastasering op afstand in de follow-up van stadium III melanoom.

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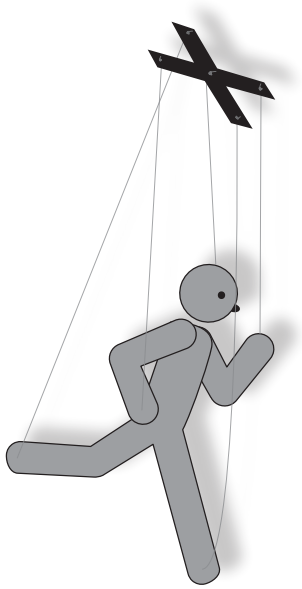
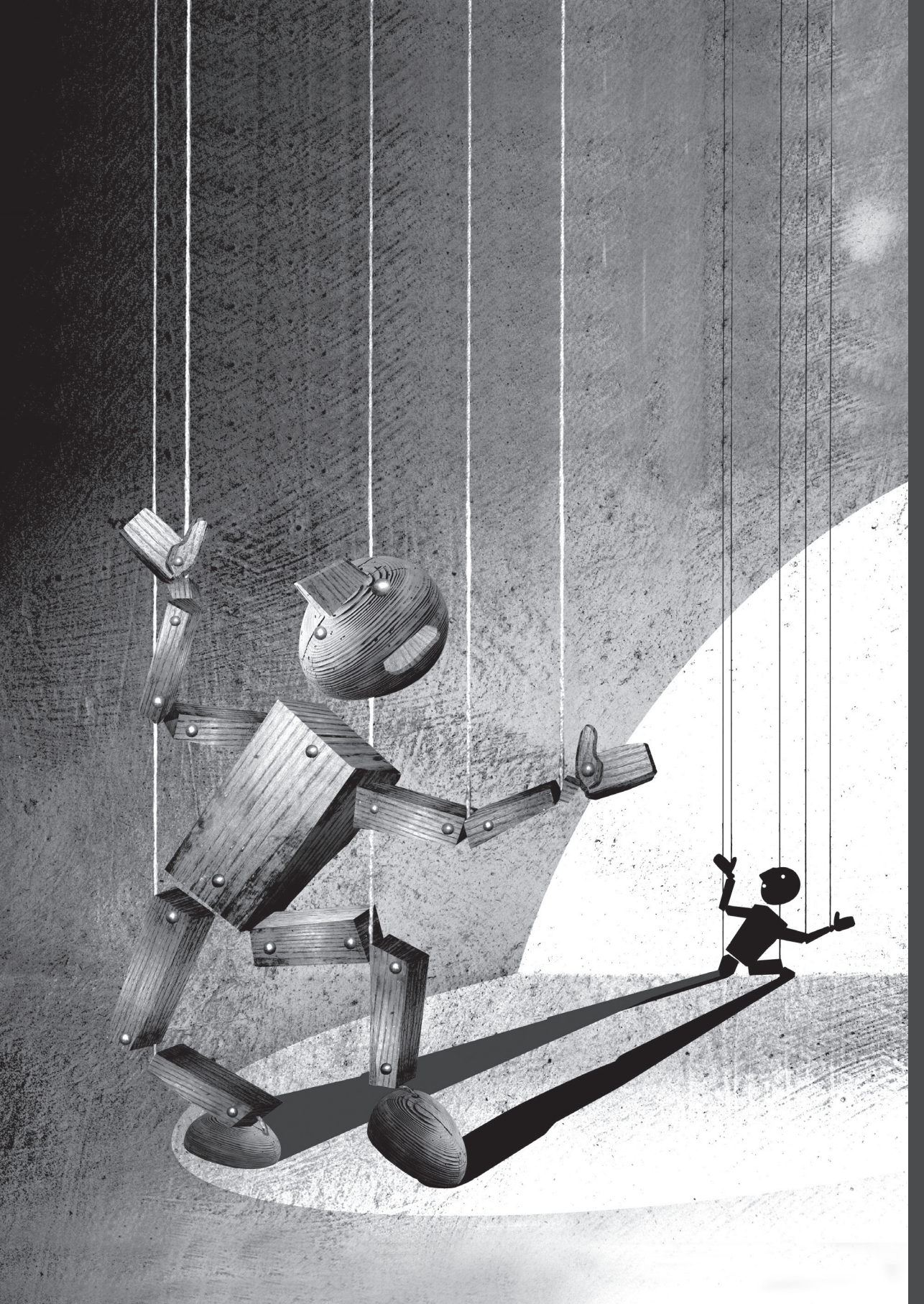
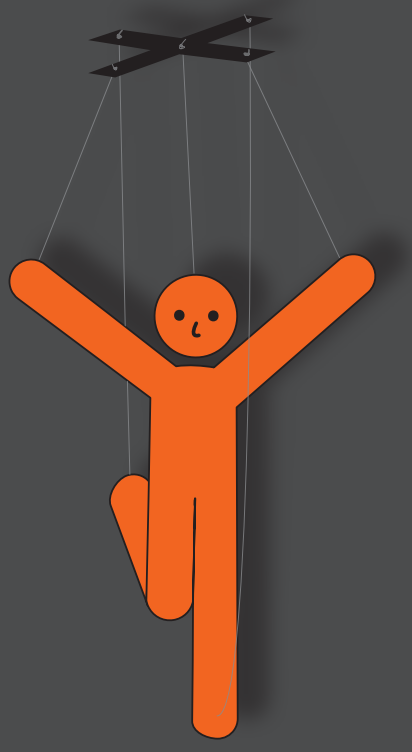




9 Future perspectives



Introduction

The pathology of melanoma, the melanotic growths in relation to their operative treatment, was described by Handley in 1907. The recommendation was made that melanomas should be excised with very wide surgical margins, 1 inch of skin and 2 inches of subcutaneous tissue.[1] Masson discovered in 1926 that the pigment cells (melanocytes) in the skin were of a neurogenic origin.[2] In 1965, Olsen suggested that there might have been a relationship with the skin nerves.[3] The hypothesis at the time was that melanoma was a tumor that emanated from the skin, did not grow through the underlying fascia and metastasized directly via the lymphatic pathways. The underlying fascia was considered more or less a natural barrier. In the 1990s, Morton called this the 'incubator' hypothesis, but he also pointed to the 'marker' hypothesis, stating that a lymphogenic and haematogenic route of metastasis existed simultaneously.[4] This explains the 'unpredictable' metastatic behavior of melanoma.

Melanoma used to be called 'melanoblastoma malignum' in the Netherlands, a rare skin tumor that was feared for surgical treatment due to the occurrence of local recurrence, intransit, regional and/or distant metastasis. Professor Pieter Kuijjer described 'melanoblastoma malignum' in a clinical lesson in Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine) in 1967, as "an extremely fascinating tumor from both a biological and a medical point of view". He advised to concentrate treatment only in a few specialized melanoma centers due to the peculiar behavior of the tumor.[5] In this regard, he seemed ahead of his time suggesting to concentrate complex cancer care. Up to the nineties, good local surgical treatment of the tumor consisted of a large excision with a margin of 5 cm because in this way the greatest chance of (local) cure was obtained and, if indicated, the resulting skin defect was covered with a free partial thickness skin graft. Primary wound closure by plastic-surgical reconstruction was dispensed with to prevent a local recurrence from not being recognized in time. The skin graft was taken from the contralateral body site to reduce the risk of recurrence in the scar. The clinical lesson ended with the following sentence "We as physicians are certainly not without influence in late stages of the disorder, but the result of rigorous therapies is still doubtful. These look like rear-guard fights".[5]

What has local, national and international melanoma research contributed to the treatment of the patient with a melanoma during the past 50 years? Is it still a lost fight or are we gaining? What are the priorities in today's (surgical-oncology) melanoma research?

History

In the past, the pathologist classified the disease melanoma by measuring the invasion depth of the melanoma in the skin according to Clark and the thickness of the melanoma in millimeters according to Breslow.[6,7] The first AJCC melanoma staging of the skin in 1992 was based on Clark level and Breslow thickness of the tumor.[8] In 2009, Clark level was removed from the AJCC staging system to be replaced by ulceration and mitosis index of the tumor (AJCC staging, 7th edition).[9]

The excision margin of the melanoma was investigated in 6 trials.[10] A meta-analysis shows that smaller margins can lead to a worse outcome than larger margins.[11] This has resulted in the following excision margins being advised based on consensus by the Dutch Melanoma Working Group: for melanomas <2mm a margin of 1 cm, for melanomas >2 mm a margin of 2 cm and for melanomas in the main neck area where margins of 2 cm are often not possible, a margin of 1 cm is sufficient if necessary.[12] After primary surgical treatment of the melanoma, a recurrence may occur in 20-28% of patients. A local or in-transit recurrence can occur in 20-28% of patients, regional gland metastases in 26-60% and remote metastases in 15-50%.[13]

Four trials showed that elective lymph node dissection resulted in no improvement in the (disease-free) survival of stage I-II melanoma. However, an increased risk of local and/or in-transit metastasis has been observed (20-30%).[14]

When Morton developed the concept of the sentinel node biopsy, melanoma surgeons had the idea that a breakthrough in the surgical treatment of the melanoma would finally be possible.[4] Indeed, we can conclude that the patient can be adequately staged with a melanoma with stage IB-II by means of a minimally invasive procedure. Unfortunately, with a positive sentinel node, performing an additional completion lymph node dissection did not seem to improve overall survival, although it did improve melanoma-specific survival.[15,16] The quality of

life of the group of melanoma patients treated with a completion lymph node dissection was better than that of a so-called 'norm group'.[17]

Arrival of the spiral Computer Tomography (CT), the Positron Emission Tomography (PET) and PET-CT made it possible to better stage patients with a regionally metastatic melanoma. A so-called upstaging took place in 27% of the patients, changing the treatment plan for one in five patients.[18,19] From now on, a 'personalized melanoma treatment' could be offered and, if necessary, a therapeutic lymph node dissection could be dispensed with and be replaced by local radiation and/or systemic treatment.

The first publication on the prognostic serum marker lactate dehydrogenase (LDH) in patients with a melanoma was published in the 1950s.[20] LDH was incorporated in the 7th AJCC staging system in 2009.[9] In human melanocytes, the protein S-100B is present.[21] S-100B is a reliable marker used to diagnose melanoma cytological- and/or histopathologically. Increase of the marker S-100B is found after brain trauma, but also in disseminated melanoma. Research over the last decades has shown that S-100B in metastatic melanoma is a much better prognostic marker than LDH.[22] In contrast to the United States, the biomarker S-100B is widely used in Europe in the follow-up of patients with melanoma in the context of personalized melanoma treatment.[23] LDH is still one of the eligibility criteria for systemic treatment trials for patients and used for response monitoring of therapy.

At the end of last century, monochemotherapy and combination chemotherapy, often darcabazine based, showed no improvement in overall melanoma survival.[24] At the same time, the delivery of high doses melphalan through hyperthermic isolated limb perfusion (HILP) as adjuvant treatment was studied. HILP with melphalan was unable to contribute to the chance to reduce in-transit metastasis.[25,26] However, HILP with melphalan is an effective regional treatment for melanoma in-transit metastases, whereas for bulky disease the combination of Tumor Necrosis Factor alpha and melphalan should be the first choice. The in-field progression-free survival after HILP is determined by the biological behavior of the intransit metastases (ITMs) and the patient's immune system.[27]

It is well know that the immune system can be activated spontaneously against melanoma. The presence of tumor infiltrating lymphocytes (TIL) in melanoma or tumor deposits is a positive prognostic sign.[28]

Morton studied the effect of intralesional injections of intradermal or subcutaneous melanoma metastases with the powerful, nonspecific immunostimulant Bacillus Calmette Guérin at the Surgery Branch of the National Cancer Institute in the 1970s.[29] However, none of the following 13 BCG-based trials in high risk patients showed impact on disease-free and overall survival, as well as other vaccine trials including Morton's promising Canvaxin trial.[30,31] At the same time, Rosenberg started the application of adoptive immunotherapy with TILs in the treatment of metastatic melanoma, at the same institute.[32]

Interferons (IFN), glycoproteins that belong to the group of cytokines play an important role in the functioning of the immune system. Interferon-alpha (IFN-α) has an anti-tumor effect, because it inhibits cell growth and simultaneously stimulates natural cancer cells. The hope was based on the immunological action of interferon. Efforts focusing upon the use of (pegylated) IFNα2b in the adjuvant treatment of high-risk melanoma patients in different schedules (high, intermediate, low dose, pegylated IFN, with or without induction phase, shorter and longer maintenance dose) were led by Kirkword and Eggermont but had generally minimal effect. Eighteen randomized controlled interferon trials were performed between 1995 and 2011. A recent meta-analysis of 15 adjuvant interferon trials showed that IFN-α significantly reduced the risk of relapse and improved survival in patients with ulcerated tumors, however lacked benefit in patients without ulceration, but showed benefit for higher doses compared to lower doses.[33] PEG-IFNα2b was approved as adjuvant treatment for high-risk resected melanoma by the FDA in 2011 and the EMA in 2012.[33]

Dendritic cells (DCs) are antigen-presenting cells and act in an immature state as sentinels of the immune system. These cells play an important role in the induction of antitumor immunity. The DC vaccines are generally well tolerated and able to induce antigen-specific T cell responses in melanoma patients. The DC vaccines in melanoma patients have not yet fulfilled their promise since the 1990s, mainly due to the lack of well-conducted phase II/III trials.[34]

Biochemotherapy, the combination of chemotherapy and immunotherapy, with dacarbazine, cisplatin and vinblastine with IL-2 and IFNα2b as immunotherapy showed also no improvement in survival.[35] Consequently, chemotherapy was only used in the palliative setting.

In the last two decades, the obtained molecular biological insights into the genesis of cancer have been the basis for the development of the so-called targeting therapy through the selective blockade of the Mitogen Activated Protein Kinase (MAPK) signal path, first with BRAF and later by a combination of BRAF and MEK-inhibitors that prevents tumor growth. This form of treatment focuses primarily on the cancer cells themselves. The treatment can also consist of immunotherapy with immune checkpoint blockade (ICB), anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and anti-programmed death (PD) - (Ligand, L). These drugs inhibit specific signals in the cancer cell that are needed for growth, division, and survival. This causes the cancer cell to die or no longer divide. In a 'Brief History of Melanoma: From Mummies to Mutations' both forms of treatment, as well as combined treatment of drug targeting and immunotherapy in melanoma are well described.[36]

The prevalence of melanoma is still increasing and with it the costs associated with follow-up after surgical treatment. In order to reduce follow-up frequency, a prospective study was initiated in the Netherlands in 2006, the MELFO-study (METc2004.127). Standard follow-up was compared with an experimental follow-up with a 27% less frequent follow-up.[37] Results showed that a reduced stage adjusted follow-up was associated with comparable recurrence rates, melanoma specific- and overall survival, and quality of life as compared to a more frequent in guidelines recommended follow-up, while a significant cost reduction of 39% was achieved, three years after diagnosis.[38]

Priorities in today's melanoma research

Prevention

The sharp increase in skin cancer in the Netherlands is explained by 1) ageing of the Dutch population, 2) depletion of the ozone layer with an increase of the intensity of UV radiation, 3) more frequent and longer skin exposure to UV radiation, 4) inside (tanning) as well as outside, and 5) spending more time outdoors due to climate changes, e.g. increase of dry and warm summers. Information about the risk of the development of the melanoma and the influence of sun and UV radiation and sensible sun protection will have to be brought to attention in the population much broader, starting in schools. The Australian government's prevention program showed this is the only way to stop the ever-increasing incidence of melanoma. The

Dutch government, health insurances, and the Dutch Cancer Society (KWF) have to play a dominant role in organizing prevention programs.
Concerned about the sharp increase of skin cancer incidence, the Ministry of Health, Welfare and Sport and the National Institute for Public Health and the Environment launched the 'UV-index action plan: version 2019' in June 2019. This UV-index action plan, aiming at drafting a joint knowledge agenda, may lead to increased knowledge of UV radiation and exposure. This will identify and prioritize topics needing extra research, in collaboration with other parties.[39]

Staging

The minimally invasive regional staging with the sentinel node biopsy was incorporated into the 8th AJCC staging system in 2017.[40] In the Netherlands, only 60% of stage IB-II melanoma patients are correctly staged with the help of a sentinel lymph node biopsy.[41] In a recent survey among surgeons and dermatologists, only twenty-five percent of these specialists agreed that the standard diagnostics of cutaneous melanoma should include a SLNB, the percentage was slightly higher amongst surgical residents (44%).[42] There is still room for further improvement.

Are there no other methods to detect the sentinel node and increase the interest of medical specialists in SLN staging? Non-invasive detection of a metastatic SLN will prevent unnecessary operations and complications, and has a direct impact on clinical decision-making.
A promising non-invasive research method appears to be the multispectral opto acoustic imaging (MSOT), which is an imaging technology that generates high-resolution optical images in scattering media, including biological tissues. MSOT illuminates tissue with light of transient energy, typically light pulses lasting 1-100 nanoseconds. The tissue absorbs the light pulses, and as a result undergoes thermo-elastic expansion, a phenomenon known as the optoacoustic or photo acoustic effect. This expansion gives rise to ultrasound waves (photoechoes) that are detected and formed into an image. Nanocolloid fluorescent indocyanine green (ICG) labeling for detection of the SLN has shown a promising sensitivity by invasive fluorescence imaging.[43-45] As ICG is a very good optoacoustic imaging agent, the straight forward labeling of 99mTc-nanocolloid just prior to injection with ICG creates the ideal dual nuclear-optoacoustic contrast agent in which we can compare Multispectral Optoacoustic Tomography (MSOT) with standard-of-care SPECT/CT imaging prior and during surgery. This form of staging is patient-

friendly and is non-invasive and thus prevents unnecessary complications and wound problems that can occur in ±10% with a minimally invasive sentinel node biopsy.[14,46] The morbidity might even be higher in people with a high body mass index and in those whose biopsy is located in the groin.
The possibilities of Positron Emission Tomography have already been discussed earlier in the staging of the melanoma with fluorine-18-deoxyglucose (FDG-PET). PET staging in melanoma is cost-effective and well established.[17,18] However, FDG is not 'melanoma specific'. Therefore, in the coming years, the PET melanoma research should be focused on the development of very specific melanoma PET tracers.[47,48] Within a few years, the UMCG will have the possibility to stage melanoma patients with a new generation total-body PET scanner that performs scans with extremely low radiation doses in potentially less than a minute. The expectation is that cancer detection will improve, and studies trafficking patterns in melanoma cell-based therapies will be possible.[49]

LDH is incorporated in the AJJC staging system since 2009.[8] Patients with a low LDH, low disease burden, and a good performance status are candidates for systemic treatment trials although S-100B might be a more sensitive biomarker for disease burden.[22] Further research with respect to both markers as well as circulating tumor DNA (ctDNA) fragments and microRNAs (miRNAs) are tools and challenges in the development of personalized melanoma treatment.

Surgery; resection margins, technique and non-surgical treatment
The optimal surgical excision margins for patients with thick (>2 mm) localised cutaneous melanomas was recently defined after an update of the Swedish trial at a follow-up of median 19.6 years; a 2-cm excision margin was safe.[50]
It is necessary that the correct excision margin of the melanoma be defined. To this end, the Melanoma Margins Trial (MelmarT) investigating 1cm vs 2cm wide excision margins for primary cutaneous melanoma was initiated in 2015 (NTC02385214). A 'MelmarT pilot' has recently been carried out examining the feasibility of a large international RCT to provide a definitive answer to the optimal excision margin for patients with a melanoma.[51] This pilot study demonstrated that a large international prospective randomized trial would be feasible to provide a definitive answer to the question of what the optimal excision margin is for patients with intermediate to high risk. However, the study has not started yet because local, national, and international governments or charity funds have not been found willing to fund

this type of surgical research. If smaller excision margins prove to be sufficient, the outcome could lead to both greater patient satisfaction due to a smaller scar and to potential cost reduction. [52] It is now or never.[53]

A number of stage III melanoma patients will have an indication for a completion or therapeutic lymph node dissection. Lymph node dissections, in particular groin nodal dissections, are associated with significant morbidity.[54] The potential of a videoscopic groin lymph node dissection is currently being investigated.[55,56] For the other regional dissections for melanoma, no new techniques are currently on the horizon. However, since 2015, the Evaluation of Groin Lymphadenectomy Extent For Metastatic Melanoma (EAGLE FM, NCT02166788) study investigates the value of a superficial versus a superficial and deep groin nodal dissection, with the primary endpoint being disease-free survival.[57]

Treatment strategies need to be developed for minimal and extensive in-transit metastasis of melanoma at the extremity and other parts of the body. Local treatment with cryosurgery, laser ablation, intra-lesional therapy (electrochemotherapy, oncolytic virus, Rose-Bengal), a single hyperthermic regional perfusion treatment with TNFa and melphalan, systemic targeted/immunotherapy therapy, or sequential are therapeutic options. Intra-lesional electrochemotherapy (ECT) is based on the local application of short and intense electric pulses in the lesions that transiently permeabilize the cell membrane. This allows the delivery of a chemotherapeutic agent directly to the cell interior.[58] Oncolytic virus therapy, based on a modified herpes simplex virus type I (talimogene laherparepvec (T-vec)), and the Rose-Bengal disodium (10% RB (PV-10)) therapy are the two main intralesional agents that are currently being investigated.[59,60] The mechanism of both intralesional therapies is cell lysis with an indirect 'bystander response' by the induction of an innate or adaptive immune response in contrast to ECT.

Systemic treatment

During the last decade, major progress has been achieved in the targeted and immunotherapy treatment of regional and disseminated melanoma resulting in improved melanoma-specific and overall survival.[61]

In metastatic disease (stage IV) and in the adjuvant setting (stage III), the prognosis is considerably improved by the targeted therapy with BRAF inhibitors (dabrafenib and vemurafenib) in BRAF mutated patients, with MEK inhibitors (trametinib

and cobimetinib) and with immunotherapy with so-called immune checkpoint inhibitors anti CTLA-4 antibody (ipilimumab) and anti-PD-1 antibodies (nivolumab and pembrolizumab). Unfortunately, these therapies also have their downsides. Only about 20% of patients benefit from one of these treatments. In other words, 80% undergo treatment that is of little to no benefit to the patient.[61] In addition, cancer research and treatment will continue to focus on adoptive cell transfer, cellular adoptive immunotherapy, and T-cell transfer therapy.
During the coming years, melanoma basic scientists, surgical oncologists, medical oncologists and pathologists will focus their melanoma research on gaining further insight into melanoma tumorbiology and the development of drugtargeting and immunotherapy in neo-adjuvant systemic treatment in the far advanced regional and metastatic melanoma. Standardizing pathologic evaluation of resected melanoma metastases following neoadjuvant-targeted or immune-checkpoint therapy is a sine qua non. The standard grading of pathologic responses will facilitate comparison of results across clinical trials and inform ongoing correlative studies into the mechanisms of response and resistance to agents applied in the neoadjuvant setting.[62]

The standard form of treatment for BRAF-wildtype patients is anti-DPD-1 (nivolumab of pembrolizumab). For these patients two options are available: targeted therapy with the combination of dabrafenib and trametinib or anti-PD-1(nivolumab, pembrolizumab).
In the coming years, melanoma research and treatment should focus on achieving durable responses in disseminated melanoma by targeted therapy, immunotherapy, chimeric antigen receptor T-cell (CAR-T) therapy and T-cell receptor (TCR) therapy and vaccines.

Cost-effectiveness
The development in the diagnosis and treatment of patients with melanoma has led to an explosive increase in the overall costs of treatment by 50 million per year in the Netherlands, mainly through the application of targeted therapy and/or immunotherapy. Only a small percentage of the melanoma patients will really benefit, for a large number treatment remains a 'rear guard fight', as Kuijjer formulated 50 years ago.[5] Therefore, research will have to focus on defining patient groups that will 'really benefit' from these new systemic treatments and studies are underway.

Patients with clinically detectable regional metastases (stage III) have a high risk to develop distant metastases. Patients with regional lymph node metastases may benefit from neoadjuvant immune therapy (ipilimumab + nivolumab).[61] Unfortunately, only one in five patients is likely to benefit from such (neo) adjuvant, toxic treatment. The OpACIN-neoadjuvant trial for clinically stage III melanoma randomly assigned patients to receive ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg, either in four adjuvant courses, or to receive the same doses split into two neoadjuvant plus two adjuvant courses. A dosing schedule of two cycles of ipilimumab plus nivolumab was less toxic, equally effective and induced a pathological response in a high proportion of patients. Only 20 percent of patients had serious side effects. With this dose schedule, the tumor had become smaller in almost 80 percent of the patients and completely disappeared in more than half of the patients.[63] This is a first step forwards in the reduction of the costs of these systemic treatments.

It is important to identify biomarkers and to understand mechanisms for response and toxicity, but also to investigate psychosocial, neurocognitive, and health-related quality of life (HRQOL) issues in advanced melanoma patients treated with immune checkpoint inhibitors.[64] The distress thermometer accompanied by the problem list and validated for the Netherlands can be an important instrument in this regard.[65] Implementing a process of screening for distress and referral need (SDRN) is feasible.[66] Patients who underwent SDRN would recommend other patients to regularly inform their health care providers about their cancer-related problems and concerns and discuss these with them.[67] The guideline Screening for distress recommends regular distress screening and timely and justified referral to psychosocial and/or paramedic health care providers of distressed patients in need of such care.[68] Optimizing patients' subjective well-being could potentially reduce the emotional, physical, and socio-economic consequences of this devastating disease.

The Dutch government will have to enter into discussions with the pharmaceutical industries and health insurance companies and the Dutch Cancer Society (KWF) to keep costs under control. In June 2019, a new financing model was proposed for expensive anti-cancer drugs, e.g. for melanoma in The Netherlands. It is a step towards 'no cure, no pay' in healthcare. Medication is only reimbursed if there is a positive response, 16 weeks after the start of initial treatment. The hope is that

expensive medicines will remain available in the Dutch health insurance system and that medication is only provided and paid for (melanoma) patients who may benefit from it.

What is the best strategy to improve OS in stage IB–II melanoma? Adjuvant therapy of high-risk stage II patients or treatment at the time of recurrence? How to select patients who will benefit from adjuvant treatment while sparing those who are unlikely to benefit from toxic effects? If melanoma biomarkers could be identified that can better predict the potential to metastasize than the current prognostic factors do, a personalized follow-up, including emotional support and patient education, could be delivered even more (cost) effectively.

Finally, with increasing prevalence, how should the follow-up of stage I-II melanoma be performed in the future? The MELFO study showed that a 'staged adjusted' follow-up is justified and leads to comparable recurrence detection, melanoma-specific and overall survival, and quality of life, and that it leads to a considerable cost reduction, one and three years after diagnosis.[36,37]
The government recommends that more oncological follow-up should be performed by the general practitioner. This is indeed a good option although GP`s are under work pressure as well.[69] The follow-up of melanoma patients can be performed by medical specialists, general practitioners and nurse-practitioners but they have to be well-educated/informed and dedicated. Melanoma-specific knowledge of the patient is important, it is the responsibility of the treating health care provider to supply patients with adequate information and to point them to reliable internet sites, such as Kanker.nl. In addition to oral and written information, e-Health videos appear to be a good supplementary and easily accessible method for informing melanoma patients.[70]
A follow-up study should be the MELFO II study in which the 'stage-adjusted' follow is further studied as the best personalized follow-up approach for stage IB–II melanoma patients. This seems justified since the patient him/herself diagnoses about 70% of the recurrences. This percentage can improve with good education of the patient and a well-conducted self-examination so that a reduced follow-up frequency will not negatively affect recurrence detection, melanoma specific and overall survival, as well as the quality of life.

Conclusion

The behavior of the melanoma is 'unimaginably unpredictable' but during the past fifty years a great deal of insight has been gained into tumor biology, surgical- and systemic melanoma treatment. In a general sense, the prognosis of melanoma in the Netherlands has improved, but this is due to the changed stage of diagnosis and thinner melanomas, rather than to improved diagnostics and/or treatment. People have become more aware of the occurrence of the disease and present themselves with a suspicious abnormality. The treatment is mainly improved due to better staging and therefore 'upstaging'.

The process to concentrate the treatment of advanced stages of melanoma in eight melanoma centers and six satellite hospitals, with specific expertise in the field of melanoma, has started. Data will be available in due course from the Dutch Melanoma Treatment Registry (DMTR) of the Dutch Institute for Clinical Auditing (DICA).[71,72] The results of the treatment of patients with metastatic melanoma are recorded in this registration and efficacy studies on the treatment of metastatic melanoma may be performed. The ultimate goal is to provide insight into the quality of melanoma care with reliable comparisons and analyses.

The next step should be to form a national melanoma research group based on the DICA principles, that is linked to the EORTC melanoma group. Only through joint regional, national and international cooperation, we can and will gain more insight into the tumor biology of the melanoma and find the optimal, personalized melanoma treatment taking quality of life and cost-effectiveness into account. Recently, the International Neoadjuvant Melanoma Consortium has been established with experts from medical oncology, surgical oncology, pathology, radiotherapy, radiology and translational research to develop recommendations for investigating neoadjuvant therapies in melanoma.[73]

The next decade, the primary role of surgery in the treatment of stage IIB and III melanoma might shift towards more targeted and/or immunotherapy based multimodality treatment. For stage IA-II melanoma patients stage-adjusted reduced follow-up seems justified and cost effective, until biomarkers to predict prognosis have been identified.[74]

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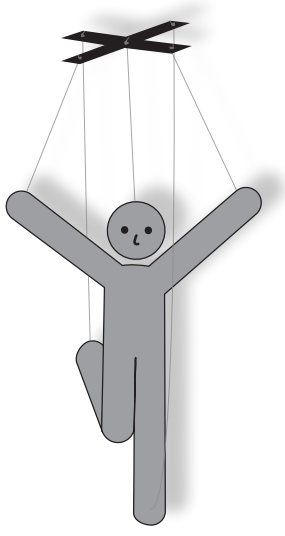

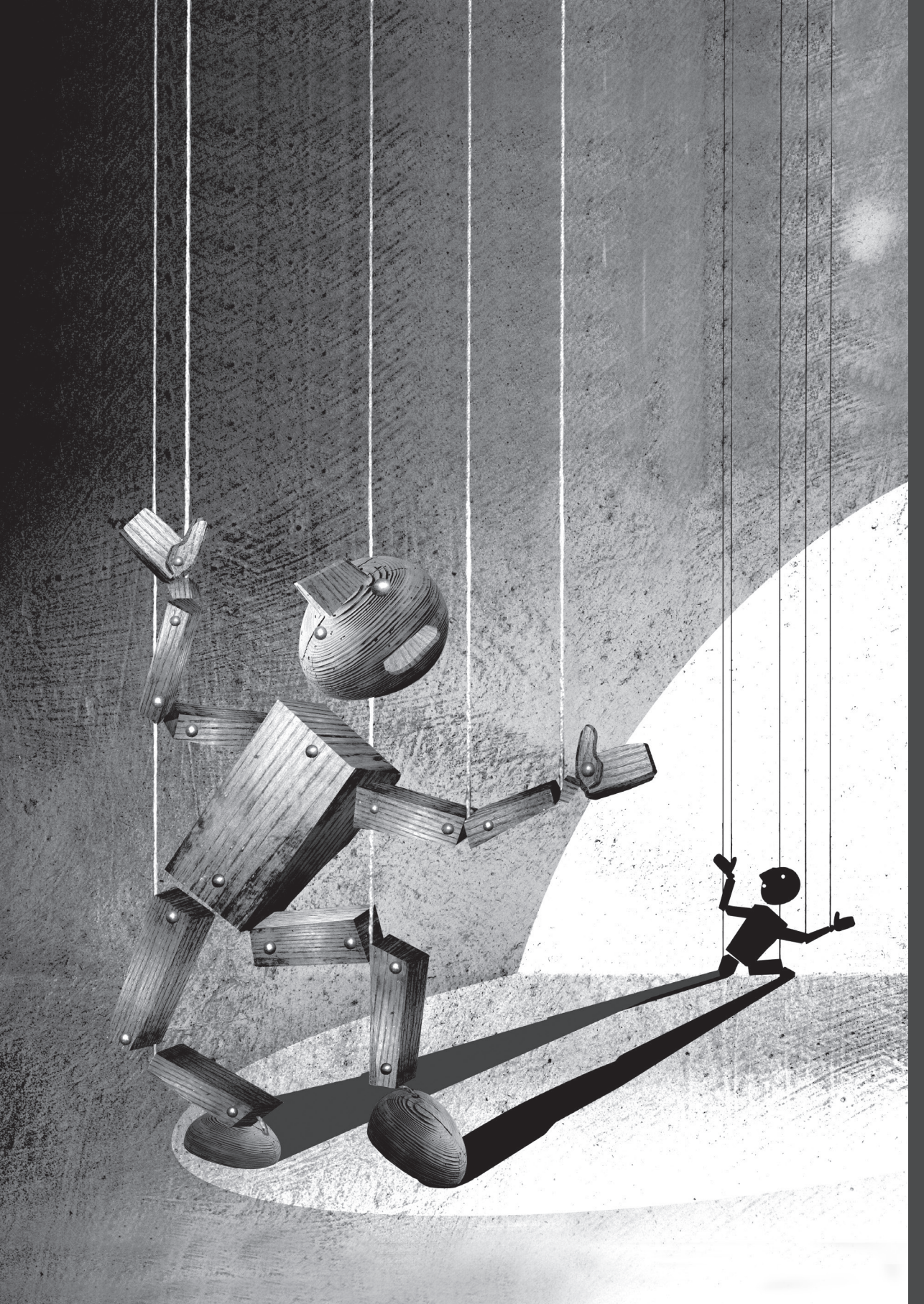

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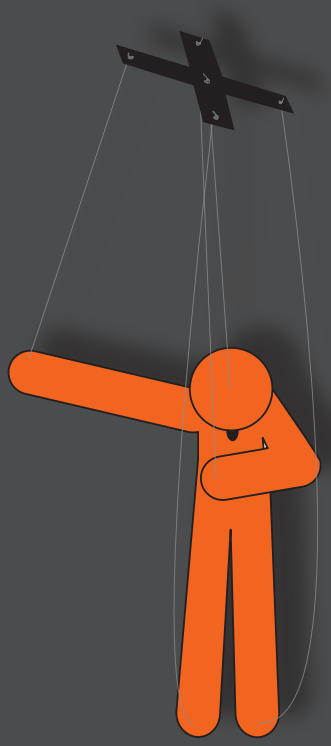
Curriculum vitae en Dankwoord



Curriculum vitae

Eric Arnoud Deckers werd geboren op 6 maart 1989 te Nieuwegein. Jongste zoon van Paul en Wies Deckers en broertje van Marc Deckers. Hij groeide op in Culemborg, vanwaar hij op 12-jarige leeftijd verhuisde naar Heerenveen. Alhier behaalde hij zijn vwo-diploma op O.S.G. Sevenwolden.

In september 2007 volgde eerst een jaar Biomedische Wetenschappen, waarna hij in 2008 hij mocht beginnen aan de studie Geneeskunde te Groningen. Na het behalen van zijn arts-examen in 2015, was hij een jaar werkzaam als ANIOS chirurgie in het Martiniziekenhuis Groningen. Dit werd gevolgd door een jaar als ANIOS chirurgie en twee jaar promotieonderzoek in het Universitair Medisch Centrum Groningen. Het promotietraject startte Eric bij de afdeling Chirurgisch Oncologie onder leiding van Prof. dr. H.J. Hoekstra.

Eric startte in september 2019 met zijn opleiding tot chirurg. Het eerste jaar in het Universitair Medisch Centrum Groningen (opleiders Dr. R.J. van Ginkel en Prof. dr. J.M. Klaase) en jaar twee, drie en vier in het Deventer Ziekenhuis (opleider Dr. R.B.M. van Tongeren).

Dankwoord

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"WE USE THE KNIFE!!!". Harald dit typeert jou als persoon, stiekem een beetje van de oude stempel. Stiekem een beetje bijzonder. Stiekem een beetje eigenwijs. Dit heeft jou echter gebracht waar jij bent en mij op wetenschapsgebied waar ik ben. Dank hiervoor!

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Dr. S. Kruijff. Filosoof. Dichter des Vaderlands. Columnist. Vader. Promotor. Copromotor. Katalysator. Beste Schelto, ik hoop dat je na mijn promotie en ons vele mailcontact mijn voornaam eindelijk goed zal schrijven, namelijk Eric met een C. Maar zonder gekkigheid: jij hebt op een bepaald moment als copromotor het strijdtoneel betreden. Hierbij diende je vooral als katalysator bij ietwat uiteenlopende meningen. Dit heeft er uiteindelijk toe geleid dat ik me heb kunnen focussen op datgene waar ik voor aangesteld was, namelijk de wetenschap bedrijven. Af en toe even bij je binnen lopen, al vond jij dat ik dat te weinig deed, waarbij ik even stoom af kon blazen. Samen bedachten we dan een manier en een oplossing. Schelto, ik wil je bedanken voor je inbreng als copromotor, je snelle respons en je rol als katalysator.

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Groningen, maart 2020

Eric