Melanoma

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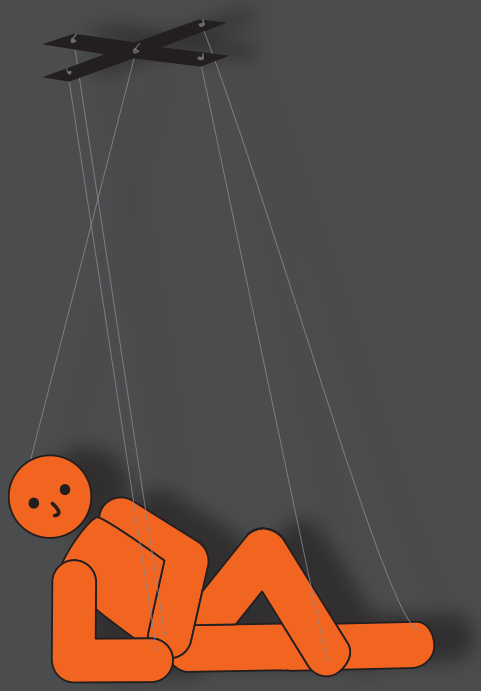
The MELFO-Study: a multi-center prospective randomized clinical trial on the effects of a reduced stage-adjusted follow-up schedule on cutaneous melanoma IB-IIC patients - results after 3-years



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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**

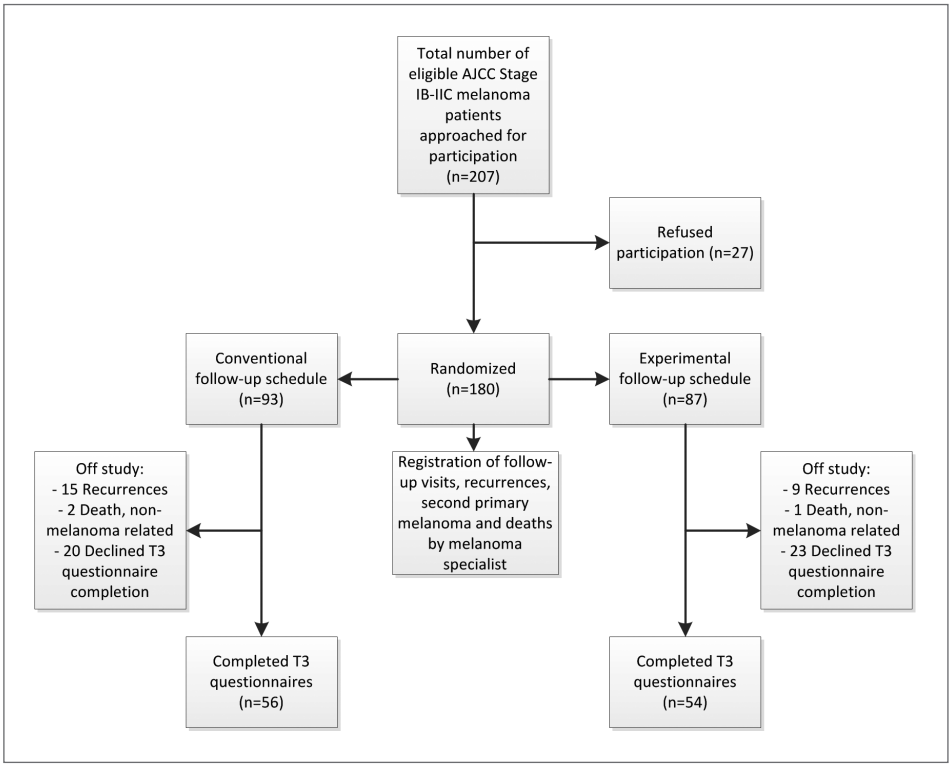

TABLE 2 **Descriptives of sociodemographic and illness-related characteristics at T1, and of follow-up related questions at T3 of the 110 participants at T3, along with comparison between study groups (CSG: n=56, ESG: n=54) at T3**

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.

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