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Follow-up Schedule for Patients With Sentinel Node–negative Cutaneous Melanoma (The MELFO Study)

An International Phase III Randomized Clinical Trial

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Objectives and Design: The MELFO (MELanoma FOllow-up) study is an international phase III randomized controlled trial comparing an experimental low-intensity schedule against current national guidelines.

Background: Evidence-based guidelines for the follow-up of sentinel node–negative melanoma patients are lacking.

Methods: Overall, 388 adult patients diagnosed with sentinel node–negative primary melanoma patients were randomized in cancer centers in the Netherlands and United Kingdom between 2006 and 2016. The conventional schedule group (control: n = 196) was reviewed as per current national guidelines. The experimental schedule group (n = 192) was reviewed in a reduced-frequency schedule. Quality of life was the primary outcome measurement. Detection rates and survival outcomes were recorded. Patient satisfaction rates and compliance with allocated schedules were compared.

Results: At 5 years, both arms expressed high satisfaction with their regimens (> 97%). This study found no significant group effect on any patient-reported outcome measure scores between the follow-up protocols. In total, 75/388 (19.4%) patients recurred, with no difference in incidence found between the 2 arms (hazard ratio = 0.87, 95% confidence interval: 0.54–1.39, $P = 0.57$). Self-examination was the method of detection for 25 experimental patients and 32 control patients (75.8% vs. 76.2%; $P = 0.41$). This study found no difference in any survival outcomes between the 2 study arms (disease-free survival: hazard ratio = 1.00, 95% confidence interval: 0.49–2.07, $P = 0.99$).

Conclusions: A reduced-intensity, American Joint Committee on Cancer (AJCC) stage-adjusted follow-up schedule for sentinel node–negative melanoma patients is a safe strategy, and patient self-examination is effective for recurrence detection with no evidence of diagnostic delay. Patients' acceptance is very high.

Keywords: cancer follow-up, detection rates, follow-up, melanoma, patient-reported outcome measures, self-examination, sentinel node biopsy, survival

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Primary cutaneous melanoma is the fifth most common cancer in both the Netherlands and the United Kingdom, accounting for 6.3% and 4.0% of all new cancer cases, respectively. Moreover, since the early 1990s, melanoma incidence rates have more than doubled in both countries.[1,2] Over the next 20 years, the worldwide incidence rates for melanoma skin cancer are projected to rise from 300,000 per year to over 450,000.[3] Melanoma disproportionately affects a younger demographic compared with other solid human cancers, with nearly half of the patients being diagnosed before their 65th birthday.[2] Furthermore, the prognosis for melanoma is generally very good, with overall 10-year survival ~90%.[4] It is estimated that ~1 in 400 adults in the United Kingdom are currently living with the diagnosis of melanoma; therefore, long-term follow-up arrangements and patient education for early detection have become key survivorship issues.

The routine use of sentinel node biopsy (SNB) to accurately stage melanoma patients has been incorporated into most international melanoma guidelines, with the main aim of identifying patients eligible for adjuvant systemic therapy.[5] However, for most patients, even those with high-risk, locally advanced primaries, the SNB shows no evidence of melanoma metastasis, though the risk of locoregional or distant spread remains a possibility for the SNB negative group, estimated as 10% to 15% at 5 years.[6]

Currently, there is no international consensus regarding either the duration or frequency of melanoma follow-up for patients with a negative SNB. Most follow-up schedules are

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based on the premise that the annual risk of recurrence increases with advancing the American Joint Committee on Cancer (AJCC) stage.[7–9] Almost 90% of recurrences occur in the first 3 years after diagnosis for intermediate and thick melanomas,[10,11] and the risk of recurrence beyond 10 years follow-up is low (2.4%).[12] For patients with thin melanomas, the risk of recurrence is very low in general, though paradoxically those patients who do go on to develop a recurrence generally present after a significant delay.[13] Accordingly, it is taxing for health care policymakers to devise follow-up schedules for melanoma patients that are not unnecessarily burdensome on secondary care resources, where the aim of such schedules is early detection of recurrences and prompt recognition of subsequent primary melanomas while providing opportunities for patient reassurance and evaluation of the outcome of surgical treatment.

The MELFO (MELanoma FOllow-up) study is an international phase III randomized controlled trial (Supplemental Digital Content 1, http://links.lww.com/SLA/E58). The aim is to provide an evidence basis for the follow-up of cutaneous melanoma patients with no evidence of metastasis following SNB. The primary endpoints of this trial are patient-reported outcome measures (PROMs) related to the quality of life (QoL), anxiety, cancer worry, and stress-related symptoms. The study was undertaken concurrently in the United Kingdom and the Netherlands, and the 3-year interim analyses concluded that the primary endpoints were not statistically different.[14,15] This final analysis addresses not only the primary endpoint at 5 years but also the predetermined intention of ultimately combining the international dataset to assess the secondary endpoints of detection rates and rate of recurrence in addition to survival outcomes (patient safety). The primary trial null hypothesis is that there is no difference in PROMs with a reduced-intensity AJCC stage-adjusted follow-up regimen when compared with the UK or Dutch national standard recommended follow-up regimen for AJCC pT1b–pT4bN0 melanoma patients staged with SNB. The secondary null hypotheses include no group differences in rates of recurrence detection and survival outcomes, in addition to schedule satisfaction and compliance.

METHODS

Study Design

Detailed methods of this multicentre, nonblinded, randomized clinical trial (ClinicalTrials.gov registration number: NCT01018004), initiated by the Department of Surgical Oncology at the University Medical Centre of Groningen (UMCG), have been described previously.[14–16] In summary, however, participants were randomized, in a 1:1 fashion, into 2 groups: one following the conventional schedule recommended in the current UK NICE or Dutch National melanoma guidelines,[17,18] and one whose follow-up was an AJCC stage-adjusted reduced schedule (Table 1). Patients were stratified by country and AJCC stage (seventh edition),[19] in 2 random permuted blocks of 4 patients, generated by a validated system (Intrialgrator) with the use of a pseudorandom number generator and a supplied seed number. Randomization and data management was centralized for all centers to the Netherlands Comprehensive Cancer Organisation (IKNL). The primary endpoint for this study was patients' QoL, reflecting anxiety, cancer worry, and stress response symptoms. Secondary endpoints included patient satisfaction and schedule compliance, recurrence rates, site of recurrence, method of detection, in addition to standard outcomes data including disease-specific survival (DSS), distant metastasis–free survival (DMFS), disease-free survival (DFS), and overall survival (OS). The study was approved in the United Kingdom by the Cambridgeshire Research Ethics Committee Service (Ref: 10/H0306/18; IRAS number: 43852) and the University Medical Centre Groningen in the Netherlands (Ref:METc2004.127).

Patients and Procedure

Inclusion criteria were SNB negative melanoma patients, AJCC stage pT1b–pT4b (seventh edition), who had undergone surgery for their primary melanoma with curative intent. Patients aged below 18 or above 85 years, those unable to complete the questionnaires for reasons of comprehension, and those who had another malignancy or previous melanoma primary were excluded from enrollment in this study.

After giving written informed consent, eligible patients were randomized as described. The setting for this trial was secondary/tertiary care melanoma referral centers in the United Kingdom and the Netherlands. All patients received oral and written information on melanoma and instructions on self-inspection of skin and draining lymph node basins. Patients completed questionnaires in English or Dutch at study entry which was shortly after diagnosis, and subsequently at 1, 3, and 5 years. The present study focuses on the final, 5-year time point with a primary endpoint of PROMs. Recurrence detection rates, survival outcomes and patient satisfaction rates, and schedule compliance were secondary endpoints. Patients discontinued the PROMs analysis following either a recurrence or subsequent primary melanoma or patient death. Surgical oncologists, dermatologists, or nurse practitioners undertook nonblinded follow-up in dedicated melanoma clinics. Follow-up consisted of comprehensive patient history and physical examination with full skin examination and reinforcement of patient education regarding skin inspection and lymph node examination. Diagnostic imaging was only performed in patients suspicious for recurrent disease, as appropriate.

Sociodemographics, Illness-related Quality of Life, and PROMs Instruments

Patients answered questions on sex, age, level of education, relationship status, daily activities, and comorbidities at T0, in addition to those regarding clarity of the patient information regarding skin inspection and lymph node examination. At T0 and 5-year time points, patients answered questions on schedule satisfaction, frequency of self-inspection, and the number of melanoma-related primary care physician (general practitioner) visits. At 5 years, questions were also asked regarding visits to the melanoma specialist in secondary care.

Patients completed the following PROMs at all time points:

(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).[20]
(2) The 3-item Cancer Worry Scale (CWS), measuring concerns about developing cancer again and the impact on daily activities.[21] 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.[22] A higher score (range 0–75) corresponds to a higher level of stress response symptoms.
(4) The RAND-36, a 36-item health-related QoL questionnaire, of which the mental component and physical component summary scores were used. The summary scores are

TABLE 1. Frequency of Follow-up Visits for the Conventional Follow-up Schedule as Recommended by the Dutch or UK NICE Melanoma Guidelines,[17,18] and a Reduced and Stage-adjusted Experimental Follow-up Schedule

Conventional Follow-up Schedule							Experimental Follow-up Schedule					
Years*	1	2	3	4	5	The Netherlands	Years*	1	2	3	4	5
AJCC Stage	Visits Per Year					Difference at 5 y (Visits, n)	AJCC Stage	Visits Per Year				
pT1b–pT2a	4	3	2	2	2	8	pT1b–pT2a	1	1	1	1	1
pT2b–pT3a	4	3	2	2	2	6	pT2b–pT3a	2	2	1	1	1
pT3b–pT4a	4	3	2	2	2	3	pT3b–pT4a	3	3	2	1	1
pT4b	4	3	2	2	2	3	pT4b	3	3	2	1	1
Conventional follow-up schedule							Experimental follow-up schedule					
Years*	1	2	3	4	5	United Kingdom	Years*	1	2	3	4	5
AJCC stage	Visits per year					Difference at 5 y (Visits, n)	AJCC stage	Visits per year				
pT1b–pT2a	4	4	4	2	2	11	pT1b–pT2a	1	1	1	1	1
pT2b–pT3a	4	4	4	2	2	9	pT2b–pT3a	2	2	1	1	1
pT3b–pT4a	4	4	4	2	2	6	pT3b–pT4a	3	3	2	1	1
pT4b	4	4	4	2	2	6	pT4b	3	3	2	1	1

*Year after surgery for primary melanoma (including staging with SNB).

standardized with a mean of 50 and a SD of 10.[23] A higher score defines a more favorable health state.

Statistical Analysis

Statistical analyses were performed using R language, version 4.1.2 (R Core Team 2021; https://www.r-project.org), Jamovi, version 1.6 (The Jamovi Project, Sydney, NSW, Australia) and Stata SE, version 12.0 (StataCorp LP, College Station, TX). The sample size and power analyses have been described previously.[16] Power analysis for a 2-sided test was performed on the STAI-state score with a power $\beta = 0.80$ and $\alpha = 0.05$. The null hypothesis was that there would be no difference in STAI between the 2 groups at 5 years. A sample size of 89 patients in each group was required for each country to prove a difference between the groups of a minimum of 4 points (norm = 36.5, SD = 9.4). The effect size (ES) of this outcome is 0.42. Patient characteristics were described, and comparisons between study groups were performed using independent Pearson χ^2, Wilcoxon, or Kruskal-Wallis tests as appropriate. *t* Tests and paired *t* tests were conducted to examine differences between groups or time differences (T0 compared with 5 years) in the PROMs analyses. 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.[24] Survival and recurrence outcomes were analyzed using Kaplan-Meier log-rank and Cox proportional hazard models. In all statistical analyses, *P* values <0.05 were considered statistically significant.

RESULTS

The enrollment of the patients and their outcomes are summarized in the CONSORT diagram (Fig. 1). In summary, between January 31, 2006, and January 8, 2016, 746 patients were screened for the study and 388 patients [192 females and 196 males; median age: 61 years (interquartile range: 50–69 years)] were enrolled (response rate: 52.0%) from the Netherlands (n = 181) and the United Kingdom (n = 207) and stratified by AJCC stage (4 levels). Overall, 196 patients were allocated to the conventional schedule group (CSG) and 192 were allocated to the experimental schedule group (ESG). Both groups were well-matched for age, socioeconomic, disability and educational levels, and tumor stage (Supplemental Table S1, Supplemental Digital Content 2, http://links.lww.com/SLA/E59). Sex was an exception, where there were significantly more females in the ESG compared with the CSG (56.8% vs 42.3%; $P = 0.004$). At the 5-year time point, 240/388 (61.9%) of patients remained on the study and completed the follow-up questionnaires. Both ESG and CSG comprised 120 patients, and Table S1 (Supplemental Digital Content 2, http://links.lww.com/SLA/E59) shows both groups were well-matched for age, socioeconomic, disability and educational levels, and tumor stage. Again, there were more females in the ESG group (59.2% vs 40.0%; $P = 0.003$). Table S1 (Supplemental Digital Content 2, http://links.lww.com/SLA/E59) demonstrates that, after 5 years, both groups expressed >97% satisfaction rate with their follow-up schedule. Most patients in both groups were continuing to examine their skin and lymph node fields regularly, and both were performing this with a similar frequency.

The overall compliance with the follow-up schedules at 5 years was 51.7% (61/120) for both groups (Supplemental Table S2, Supplemental Digital Content 2, http://links.lww.com/SLA/E59). No significant differences between the groups were detected in terms of the number of unscheduled or missed follow-up appointments. In approximately half of the patients, the additional visit was confined to one isolated episode in 5 years.

Patient-reported Outcome Measures

In total, 240 patients (120 in each study arm; 135 patients from the United Kingdom and 95 from the Netherlands) completed their PROMs questionnaires. Table 2 shows the results of the PROMs analyses in this group, both at enrollment/baseline (T0) and at 5 years. At T0, there were no significant differences between the 2 groups in terms of PROMs. At 5 years, no significant group effect was found on the IES, CWS, STAI, and RAND-36 scores indicating no reported difference in PROMs between the follow-up protocols. When comparing T0 and 5 years PROMs data, patients in the CSG reported a significant improvement of the CWS and IES for the CSG ($P < 0.001$, both) indicating that they were experiencing less stress response symptoms and worry related to their cancer after 5 years as compared with shortly after diagnosis. The ES calculations (Cohen *d*) indicated that

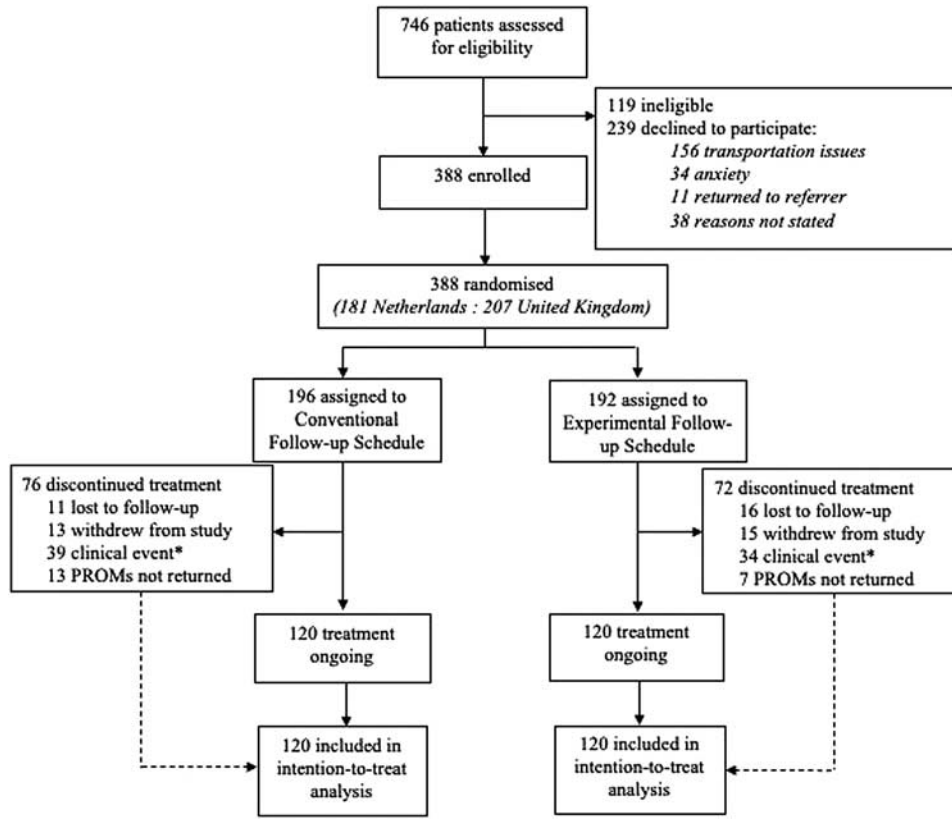

FIGURE 1. Consort flow diagram for the MELFO study. *Clinical event = melanoma recurrence or diagnosis of second primary melanoma or death from any cause.

the clinical importance of these differences was "large" in both measures (ie, >0.5). In the ESG group, patients reported a significant improvement in anxiety, cancer worry and impact of event scores at 5 years compared with baseline ($P < 0.001$, all 3 scores), indicating that the ESG were experiencing less anxiety, cancer worry and stress response symptoms after 5 years. The ES calculations indicated that the clinical importance of these differences was "moderate" for the STAI and CWS scores and "large" for the IES score. At 5 years, both groups reported significantly improved mental and physical states of health compared with the baseline measurements. ES calculations indicated that the clinical importance of the observed statistically significant between-group difference RAND-36 QoL was "small" (ie, <0.3 in all measures).

TABLE 2. Patient-reported QoL Outcome Measures at Baseline and After 5 Years—United Kingdom and The Netherlands Combined

Questionnaire	Study Group	Baseline [Mean (SD)]*	5 y [Mean (SD)]	Study Group (P†) 0 y	Study Group (P†) 5 y	Baseline−5 y (P‡)	Effect Size§
STAI							
	Conventional	32.4 (7.6)	31.3 (8.2)	0.68	0.48	0.15 (conventional)	0.139
	Experimental	32.9 (8.2)	30.4 (7.9)			0.001 (experimental)	0.311
CWS							
	Conventional	7.8 (2.7)	6.3 (1.7)	0.11	0.56	<0.001 (conventional)	0.665
	Experimental	7.2 (3.1)	6.1 (2.1)			<0.001 (experimental)	0.415
IES							
	Conventional	27.7 (9.7)	20.2 (6.9)	0.13	0.60	<0.001 (conventional)	0.891
	Experimental	25.7 (9.8)	20.7 (8.0)			<0.001 (experimental)	0.559
RAND-36 Mental Component							
	Conventional	50.6 (9.9)	52.5 (8.5)	0.86	0.70	0.06 (conventional)	−0.206
	Experimental	50.4 (10.3)	52.9 (8.1)			0.003 (experimental)	−0.270
RAND-36 Physical Component							
	Conventional	49.1 (9.4)	51.6 (11.6)	0.12	0.19	0.02 (conventional)	−0.237
	Experimental	47.1 (10.6)	49.8 (10.1)			0.004 (experimental)	−0.261

*For patients who also filled in the questionnaire at 5 years.
†t test.
‡Paired t test.
§Cohen d.

Subgroup analysis of the PROMs data, stratified by country, revealed similar results (Supplemental Table S3, Supplemental Digital Content 2, http://links.lww.com/SLA/E59).

Recurrence Detection and Survival Outcomes

At 5 years follow-up, outcome data was available for 386 patients (99.5%). Table 3 outlines the univariate and multivariate outcomes analyses for the study period, and Figure 2 demonstrates the Kaplan-Meier survival curves for each survival endpoint recorded during the trial, stratified by randomization arm. During follow-up, 43 patients had died, including 20 patients in the ESG cohort and 23 patients in the CSG cohort. Most of the deaths were melanoma-specific (33/43; 76.7%), with 18/23 (78.3%) in the CSG and 15/20 (75%) in the ESG. There was no difference in OS [hazard ratio (HR) = 0.90, 95% confidence interval (CI): 0.49–1.66, $P = 0.74$] or melanoma-specific survival (HR = 0.85, 95% CI: 0.42–1.72, $P = 0.66$) between the 2 groups. The 5-year DFS was 80.3% (95% CI: 74.6%–86.5%) for the CSG and 82.7% (95% CI: 76.9%–88.9%) for the ESG, with an identical 5-year DMFS of 87.1% for both study groups (HR = 0.99, 95% CI: 0.54–1.82, $P = 0.98$).

Table 4 outlines the recurrence details and detection data with subsequent treatments. In total, 59 recurrences and 16 new melanoma primaries were detected during the study period. In both groups, 75% or more of the detections were initially by the patient. The 5-year cumulative hazard for detection of recurrence or new primary melanoma was 22.3% (95% CI: 15.8%–28.2%) for the CSG and 18.5% (95% CI: 12.2%–24.3%) for the ESG, with a HR of 0.86 (95% CI: 0.54–1.36; $P = 0.51$). There was no significant difference between the 2 groups in terms of stage of detection nor subsequent first-line treatment of patients following tumor recurrence.

Multivariate analysis demonstrated that primary tumor Breslow thickness and ulceration status were independent predictors of melanoma-specific survival, whereas patient age and sex, in addition to the allocated study arm and the enrolling country were not. Similar results were seen for the other 4 survival outcomes measured, namely OS, DMFS, DFS, and detection-free survival (Table 3).

DISCUSSION

This current study has shown that, 5 years after staging with a negative SNB, AJCC pT1b–pT4bN0 cutaneous melanoma patients assigned to the reduced, stage-adjusted follow-up schedule (ESG) reported no difference in levels of anxiety, cancer worry, and stress response symptoms, in addition to physical and mental health-related QoL when compared with those reported

TABLE 3. Univariate and Multivariate Survival Outcomes Analyses

Survival	Subgroup	HR (95% CI) Univariable	HR (95% CI) Multivariable
DSS			
Country	The Netherlands	Referent	Referent
	United Kingdom	1.03 (0.51–2.07), $P = 0.94$	1.07 (0.52–2.20), $P = 0.85$
Randomization arm	Conventional	Referent	Referent
	Experimental	0.85 (0.42–1.72), $P = 0.66$	1.00 (0.49–2.07), $P = 0.99$
Sex	Female	Referent	Referent
	Male	1.94 (0.93–4.02), $P = 0.076$	1.53 (0.71–3.31), $P = 0.28$
Ulceration	Absent	Referent	Referent
	Present	3.47 (1.73–6.96), $P < 0.001$	2.15 (1.03–4.48), $P = 0.042$
Age (y)	Mean: 58.3	1.03 (1.00–1.06), $P = 0.051$	1.01 (0.98–1.04), $P = 0.52$
Breslow thickness (mm)	Mean: 2.0	1.50 (1.34–1.68), $P < 0.001$	1.41 (1.24–1.61), $P < 0.001$
DFS			
Country	The Netherlands	Referent	Referent
	United Kingdom	0.81 (0.49–1.31), $P = 0.39$	0.90 (0.54–1.49), $P = 0.69$
Randomization arm	Conventional	Referent	Referent
	Experimental	0.89 (0.55–1.46), $P = 0.65$	0.92 (0.56–1.53), $P = 0.76$
Sex	Female	Referent	Referent
	Male	1.33 (0.81–2.17), $P = 0.26$	1.13 (0.68–1.90), $P = 0.64$
Ulceration	Absent	Referent	Referent
	Present	3.86 (2.36–6.32), $P < 0.001$	2.52 (1.51–4.23), $P < 0.001$
Age (y)	Mean: 58.3	1.03 (1.01–1.05), $P = 0.012$	1.01 (0.99–1.03), $P = 0.28$
Breslow thickness (mm)	Mean: 2.0	1.43 (1.31–1.55), $P < 0.001$	1.35 (1.23–1.49), $P < 0.001$
Detection-free*			
Country	Netherlands	Referent	Referent
	United Kingdom	0.78 (0.50–1.23), $P = 0.29$	0.79 (0.49–1.27), $P = 0.34$
Randomization arm	Conventional	Referent	Referent
	Experimental	0.86 (0.54–1.36), $P = 0.51$	0.87 (0.54–1.39), $P = 0.57$
Sex	Female	Referent	Referent
	Male	1.30 (0.82–2.06), $P = 0.26$	1.09 (0.68–1.77), $P = 0.72$
Ulceration	Absent	Referent	Referent
	Present	2.47 (1.54–3.96), $P < 0.001$	1.61 (0.97–2.66), $P = 0.063$
Age (y)	Mean: 58.3	1.03 (1.01–1.05), $P = 0.002$	1.02 (1.00–1.04), $P = 0.053$
Breslow thickness (mm)	Mean: 2.0	1.36 (1.25–1.48), $P < 0.001$	1.30 (1.18–1.43), $P < 0.001$

*Risk of detection of recurrence or second primary melanoma.
DFS indicates disease-free.

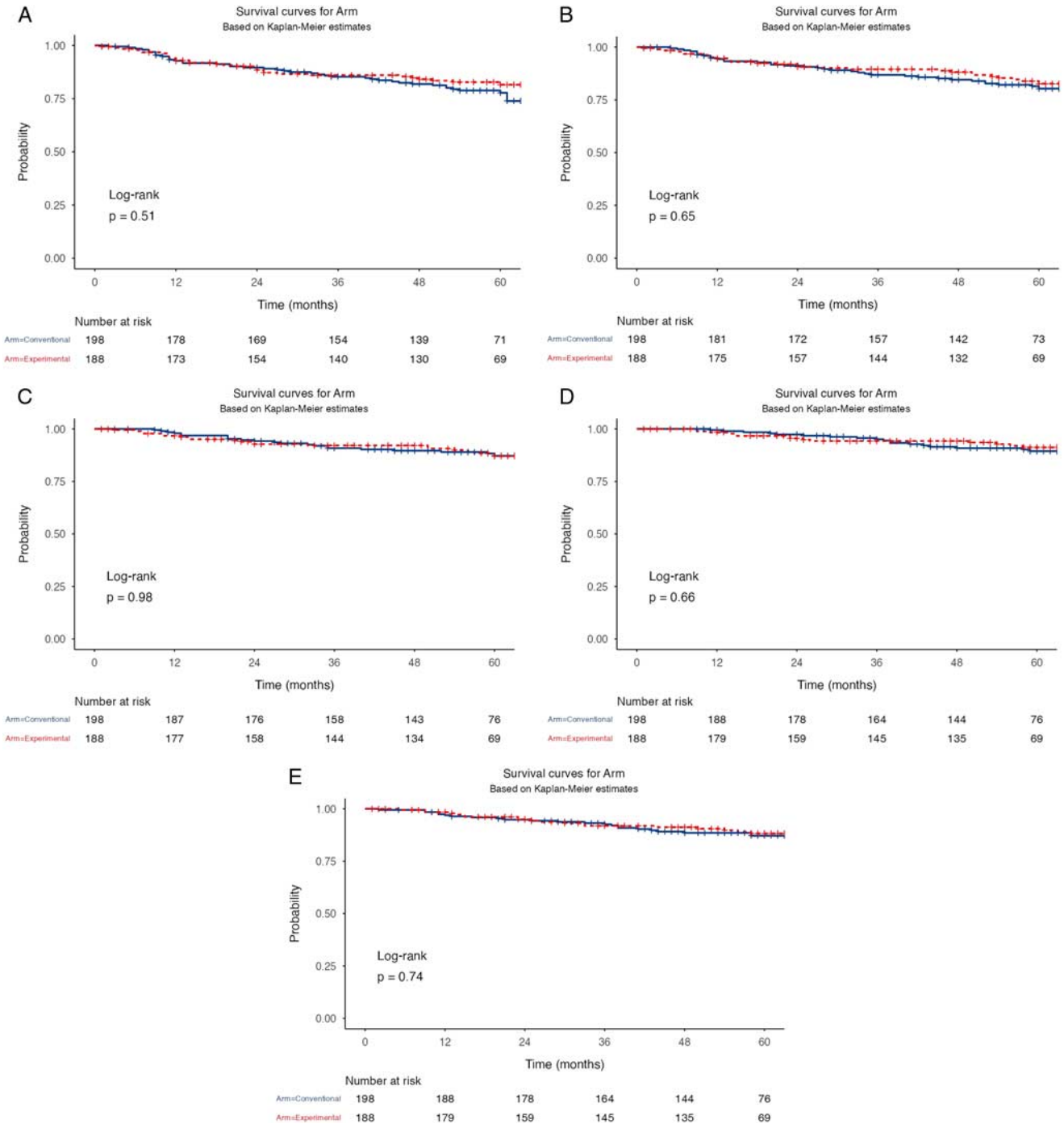

FIGURE 2. Kaplan-Meier survival curves showing survival outcomes stratified by study arm allocation. A, Detection-free survival. B, DFS. C, DMFS. D, Melanoma-specific survival. E, OS.

by the patients assigned to the nationally prescribed follow-up schedules of the United Kingdom or Netherlands (CSG).[17,25] This study demonstrated that the reduced follow-up schedule was also safe, with no difference in recurrence detection rates, DFS, DMFS, or DSS. These results support the hypotheses of no differences in PROMs, patient satisfaction, detection rates, recurrences, and deaths between study groups.

Quality of Life and Patient-reported Outcome Measures

It was felt appropriate for the trial design to be replicated in 2 countries to validate the PROMs findings for populations with different languages, albeit with similar cultural backgrounds and socioeconomic standing internationally. Combining the data from the 2 studies allowed for an appropriately powered

TABLE 4. Recurrence Data, Stratified by Randomization Arm

Variables	N* = 75	n/N (%) Conventional (n = 42)	n/N (%) Experimental (n = 33)	Test Statistic
Country: United Kingdom	75	19/42 (45.2)	18/33 (42.9)	$\chi^2_1 = 0.64$, $P = 0.42$†
Sex: female	75	16/42 (38.1)	16/33 (48.5)	$\chi^2_1 = 0.82$, $P = 0.37$†
Age	75	51.0 (66.0–73.1)	62.3 (69.0–73.7)	$F_{1,73} = 0.99$, $P = 0.32$‡
Primary site	75			$\chi^2_3 = 2.77$, $P = 0.43$†
Head and neck		7/42 (16.7)	2/33 (6.1)	
Lower limb		14/42 (33.3)	13/33 (39.4)	
Torso		15/42 (35.7)	15/33 (45.5)	
Upper limb		6/42 (14.3)	3/33 (9.1)	
AJCC stage (eighth edition)	75			$\chi^2_4 = 1.99$, $P = 0.58$†
pT1b–pT2a		13/42 (31.0)	14/33 (42.4)	
pT2b–pT3a		11/42 (26.2)	9/33 (27.3)	
pT3b–pT4a		12/42 (28.6)	8/33 (24.2)	
pT4b		6/42 (14.3)	2/33 (6.1)	
Median detection free interval (mo)	75	10.0 (26.0–43.2)	10.0 (19.0–35.7)	$F_{1,73} = 0.64$, $P = 0.43$‡
Method of detection	75			$\chi^2_2 = 1.81$, $P = 0.41$†
Patient		32/42 (76.2)	25/33 (75.8)	
Partner		2/42 (4.8)	0/33 (0.0)	
Clinician		8/42 (19.0)	8/33 (24.2)	
Means of detection	60			$\chi^2_2 = 2.22$, $P = 0.33$†
Examination		23/35 (65.7)	12/25 (48.0)	
Symptoms		8/35 (22.9)	10/25 (40.0)	
Other		4/35 (11.4)	3/25 (12.0)	
Site of first detection	75			$\chi^2_4 = 1.62$, $P = 0.80$†
In-transit		7/42 (16.7)	8/33 (24.2)	
Regional		9/42 (21.4)	6/33 (18.2)	
Distant		13/42 (31.0)	9/33 (27.3)	
Second melanoma		8/42 (19.0)	8/33 (24.2)	
Multiple sites		5/42 (11.9)	2/33 (6.1)	
Size: Large (>2 cm maximum diameter)	52	12/29 (41.4)	11/23 (47.8)	$\chi^2_1 = 0.22$, $P = 0.64$†
First-line treatment after recurrence	67			$\chi^2_5 = 2.78$, $P = 0.73$†
Surgery		23/38 (60.5)	18/29 (62.1)	
Surgery with radiotherapy		4/38 (10.5)	1/29 (3.4)	
Radiotherapy only		3/38 (7.9)	2/29 (6.9)	
Immunotherapy		1/38 (2.6)	2/29 (6.9)	
Chemotherapy		6/38 (15.8)	6/29 (20.7)	
Regional limb infusion		1/38 (2.6)	0/29 (0.0)	
First-line treatment intent	73			$\chi^2_2 = 2.73$, $P = 0.26$†
Curative		27/40 (67.5)	19/33 (57.6)	
Palliative		12/40 (30.0)	10/33 (30.3)	
Observation		1/40 (2.5)	4/33 (12.1)	

*N is the number of nonmissing values.
†Pearson test.
‡Kruskal-Wallis test.

analysis at 5 years. Previously published results of the interim analysis of both studies at 3 years demonstrated the highly correlated data between the 2 countries.[14,15]

After 5 years of follow-up, 240 (61.9%) completed and returned the PROMs questionnaires. The overwhelming majority (>97%) of patients remained satisfied with their follow-up schedule, regardless of the frequency of clinic visits. Over the 5-year period, the compliance among the patients with their allotted schedule was 51.7%, with most (~90%) noncompliant patients requesting additional visits rather than missing them. Of those patients who did access an additional clinic, over 50% of the patients did this only once, while very few patients (<5%) had visited their general practitioner in the preceding 6 months. Our data suggest that the reason for these extra visits may be increased awareness of suspicious lesions, possibly resulting from effective education on self-inspection and self-examination.

Previous analyses of the data in the Netherlands and the United Kingdom showed that both sets of patients demonstrated significantly reduced levels of worry and cancer stress response symptoms after the initial twelve months of follow-up, which then persisted through to 3 years.[14,15] This final study demonstrated significant reported improvements in anxiety, cancer worry, and impact of event scores for both groups of patients at 5 years compared with baseline, with the ES calculations indicating these findings as clinically important. Similarly, the QoL analyses indicated that both subgroups reported an overall improvement in their mental and physical health at 5 years compared with baseline.

Previous studies have suggested that 50% of patients report having high levels of anxiety before and during outpatient clinic visits.[26] Our data suggest that the stress response, anxiety and worry symptoms decrease over time from diagnosis, regardless of the frequency of the follow-up schedule, particularly where no recurrence is detected. ES calculations showed that the reported improvements range in clinical importance from moderate to high in both groups.

Safety

At 5 years of follow-up, our results show that the number of recurrences and second primary melanomas and the time until detection for patients with AJCC stage pT1b–pT4bN0 was independent of the assigned follow-up schedule. Over half (41/75) of the recurrences were detected within the first 2 years, which is consistent with previous literature.[10,11,27,28] This study also showed that patients are most likely to detect their recurrences first, with 76.0% (57/75) of all recurrences detected this way, a finding that is consistent with observations of previously published studies.[10,11,26] It is striking that this proportion is virtually identical for both subgroups regardless of the frequency of scheduled clinic visits the patient attended. It is also reassuring that the data confirms that the recurrences were detected at the same stage in both groups, with many patients presenting with treatable disease progression and ~30% of patients presenting with unresectable disease managed with palliative intent. Crucially there was no evidence of diagnostic delay, with the recurrence-free survival intervals identical in both groups. Overall, the 5-year recurrence rate in this study was 17.1%, which is comparable to previously published literature.[6] Accordingly, we conclude from our results that the experimental, lower-frequency follow-up regimen is safe in terms of recurrence detection and patient outcome.

Limitations

Our protocol did not mandate any radiological surveillance of the patients since there is/was no consensus on the topic. Regardless, most melanoma patients are pT1b–pT3aN0 (81.4% of this cohort) after staging with SNB, and these patients are unlikely to qualify for either adjuvant systemic treatment or routine systemic radiological surveillance for the foreseeable future; therefore, our findings are still highly relevant to current clinical practice, though not for those sentinel node–negative patients receiving adjuvant systemic therapy.

Due to the pragmatic design and the open access clinic policy mandated by both the trial protocol and the ethics committee, nearly half of the patients did not strictly adhere to the follow-up protocol. Similarly, the nonreturn rates for the PROMs questionnaires at 1, 3, and 5 years were 11%, 18%, and 38.1%, respectively, though power analysis showed that 89 patients per study arm were needed to assess the primary endpoint, which was achieved. Encouragingly, no differences in sociodemographic and illness-related variables were found between the participants in the 2 study groups at 5 years. A formal health economics analysis complimenting this study would have been desirable, but funding constraints did not allow for this. However, the Dutch investigating group reported costs per patient were 39% lower in the ESG.[15] In reality, the findings of our study indicate a potential freeing up of patient episodes in busy outpatient clinics, which we estimated crudely as an average of 32 patient episodes per month in the United Kingdom for a center undertaking 200 SNBs per annum (Table 1). Finally, the AJCC seventh edition which was superseded by the eighth edition during trial follow-up. The data has been analyzed and presented according to the eighth edition to make the data contemporaneous. The groups remain well-matched (Table S1, Supplemental Digital Content 2, http://links.lww.com/SLA/E59), and we have reported the survival outcomes in terms of Breslow thickness and ulceration status, which we believe mitigates any concerns regarding this approach.

CONCLUSIONS

The results of this international, multicentre, phase III randomized controlled trial, undertaken in both Dutch and English-speaking cohorts, provide evidence that clinical follow-up for sentinel node–negative, AJCC stage pT1b–pT4bN0 melanoma patients with a reduced stage-adjusted follow-up schedule remains an appropriate and safe approach in terms of mental and physical QoL, patient satisfaction and recurrence detection rates over 5 years. There was no evidence that a reduced follow-up regimen resulted in the diagnostic delay or worse patient outcome. We advocate that the key to a successful follow-up regimen is patient education in terms of skin and nodal field self-examination with the opportunity for the patient to initiate prompt follow-up if they are concerned.

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