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Health-related quality of life in patients with melanoma expressed as utilities and disability weights

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Summary

Background Few studies about health-related quality of life (HRQoL) in patients with melanoma have expressed their results in terms of utilities or disability weights (DWs). Utilities are required for calculating quality-adjusted life years and therefore for cost-effectiveness analyses. DWs are useful to assess the burden of diseases through disability-adjusted life years.

Objectives To provide utilities and DWs regarding patients with melanoma.

Methods The patients were classified into eight groups using four stages based on the 2009 American Joint Committee on Cancer stages, with each stage subdivided into treatment and remission phases. The EuroQoL Five Dimensions Five Levels (EQ-5D-5L) questionnaire was completed by the patients with melanoma to provide a mean utility for each group. In addition to this, the EuroQoL visual analogue scale (VAS) and a validated quality-of-life questionnaire dedicated to patients with melanoma [Functional Assessment of Cancer Therapy Melanoma (FACT-M)] were completed by the same patients in order to compare their results with the obtained utilities. DWs were obtained by calculating, for each patient, the difference between his/her utility and the corresponding sex- and age-specific population norm.

Results A total of 395 questionnaire sets were completed. Utilities and DWs showed significant differences between follow-up groups. Treatment groups had similar utilities and DWs but these results were obtained during different treatment durations and therefore have different weights. The VAS and the FACT-M were found to be less sensitive. Nevertheless, the FACT-M identified some problems not found by the EQ-5D-5L questionnaire.

Conclusions The EQ-5D-5L questionnaire seems adequate to provide utilities and DWs in patients with melanoma. Lower HRQoL in female patients with melanoma is probably linked to lower HRQoL in the general population.

What's already known about this topic?

- Utilities and disability weights (DWs) are essential for cost-effectiveness analyses (CEAs) and disease burden assessments.
- However, the utilities currently available for patients with melanoma are based on small sample sizes and the available DWs are obsolete.

What does this study add?

- Based on the analysis of 395 EQ-5D-5L questionnaires, we provide new utilities and DWs regarding patients with melanoma using a four-stage grouping based on the 2009 American Joint Committee on Cancer classification (0–IA, IB–II, III and IV), with each stage being subdivided into treatment and remission phases.
- The results, which are in line with other previous studies conducted with other instruments, can be essential for further melanoma CEAs and burden assessments.

Many studies of health-related quality of life (HRQoL) in patients with melanoma are available, including review articles.[1–3] Nevertheless, most of these studies use methods that do not express their results as utilities and are therefore of little value for cost-effectiveness analyses (CEAs).

Medicoeconomic aspects are being taken into consideration more frequently for melanoma, from detection to treatment. In CEA, effectiveness is measured in terms of quality-adjusted life years (QALYs) which requires HRQoL values between 0 (death) and 1 (perfect HRQoL). These values, referred to as 'utilities', are obtained through so-called generic methods. EuroQoL Group provides a Five Dimensions questionnaire (EQ-5D), one of the most common generic methods, to be used in combination with their visual analogue scale (VAS).

In addition to these generic methods, various nongeneric methods are available. Among these, the Functional Assessment of Cancer Therapy Melanoma (FACT-M) is the only validated method dedicated to patients with melanoma.[4]

The utilities currently available for patients with melanoma were calculated based on a rather small number of patients, and were published with very few details. Two posters based on only 101 patients who were categorized into six groups[5,6] provided utilities that were used in several melanoma CEAs.[7–10] The same team subsequently published a pilot study that included 163 patients who were classified using eight stages, although five of these stages contained fewer than 12 patients.[11]

In addition to the concept of QALY used in CEA, the disability adjusted life years (DALYs) measurement has been designed to calculate and compare the burden of diseases. For DALY calculations, HRQoL is expressed as a number between 1 (death) and 0 (perfect HRQoL) and is referred to as a disability weight (DW). Usually, DWs are assessed in people who do not necessarily have the studied health state, but the EQ-5D method has been used as well.[12–15] The available melanoma-specific DWs were published in 1997 before the generalization of sentinel node biopsy (SNB) and the emergence of new therapies in stage IV melanomas.[16] They were recently used to assess the increase of overall melanoma burden in the Netherlands over 10 years.[17] However, they appear to be suboptimal for assessing the current melanoma burden per stage.

The main aim of the present study was to provide mean utilities and DWs regarding patients with melanoma who were categorized into eight groups using a four-stage grouping based on the American Joint Committee on Cancer (AJCC) classification (7th edition, 2009) (0–IA, IB–II, III and IV), with each stage being subdivided into treatment and remission phases. For this purpose, we collected 395 EQ-5D-5L questionnaires (5L indicating 5 levels).[18] The same patients completed the VAS and the FACT-M questionnaire. The secondary aim of the study was to compare the results obtained with these three methods.

Patients and methods

The study was approved by the ethics committee of the Université catholique de Louvain (number B403201214566).

Patients

All eligible patients (see criteria below) seen in our melanoma clinic were asked to participate in the present study by completing a set of questionnaires. The inclusion period ran from 1 July to 31 December 2012. An extra inclusion period only for patients in treatment ran from 1 January to 15 May 2013. Eight groups of patients were created according to the stage of their illness and the time since their last treatment.

The AJCC classification was the reference for the staging.[19] Patients with stage 0 and IA melanoma were pooled because of the marginal differences regarding surgical treatment and follow-up. Patients with stage IB and II melanoma were also pooled because these patients had undergone SNB that had not been followed by elective node dissection and because surgical resection margins do not seem to influence HRQoL.[20]

Utilities and DWs are classically assessed for 1 year with an assumed stable health state. Such assessment can be relatively easy in the presence of chronic diseases[21] but melanoma treatment, when only surgical, is generally much shorter than 1 year. Therefore, we chose to consider treatment durations (assessed by experts) specific for each stage that included surgical treatment (Table 1). Some of our utilities and DWs are therefore applicable only for a duration given in months, and can be used to calculate QALY or DALY, knowing that 1 month is equal to one-twelfth of a year. The time frames for questionnaire completion (Table 1) were based on expert opinion that these time frames correspond to the mean

Table 1 Treatment and remission durations, time frame for the completion of questionnaires

	Assessed treatment duration	Assessed time frame after treatment for the completion of questionnaires	Assessed remission duration	Time frame for the completion of questionnaires
Stages 0–IA	1 month	7–10 days	2 years	Inclusion period
Stages IB–II	2 months	10–20 days	2 years	
Stage III	3 months	15–30 days	N/A	
Stage IV	N/A	Inclusion period	N/A	

N/A, not applicable: there is no assessment, the duration is real.

HRQoL experienced for the three respective treatment durations. The exact day within the interval was the day of a follow-up visit.

Even if the follow-up was lifelong for all stages, the HRQoL was studied during a period of only 2 years of follow-up in patients with stage 0–II melanoma because it has been shown that after 2 years, HRQoL is not worse than in the general population.[22] After a 2-year follow-up, these patients with stage 0–II melanoma were therefore excluded from the study. Very few patients with stage II or III melanoma received adjuvant interferon in our clinic because we suggested it only for some patients with ulcerated primary melanomas.[23] The only patient treated with interferon was excluded from the study because his treatment was much longer than 3 months. Patients with stage IV melanoma in remission but still under treatment were classified as patients under treatment because we wanted to take into account the side-effects of the treatment. Most patients completed the questionnaire only once; however, patients seen in different phases (treatment vs. follow-up) and/or stages during the inclusion period were asked to complete the same questionnaire twice.

The aim of the study was explained orally to each patient by the main investigator (I.T.) or, less frequently, by another physician or a nurse at the melanoma clinic. Upon consenting to participate in the study, patients were asked to sign an informed consent form.

Questionnaires

Three questionnaires were submitted to each patient: EQ-5D-5L, VAS and FACT-M.

EQ-5D-5L is a validated questionnaire developed by EuroQol.[18] It studies HRQoL through five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. By choosing between five levels in each dimension (no, slight, moderate, severe or extreme problems), each patient self-reports his/her HRQoL for the day on which the questionnaire is completed. EQ-5D-5L was chosen because it has an improved discriminatory power and a smaller ceiling effect than EQ-5D-3L.[24] The VAS is a simple scale on which the patient has to put a cross in the appropriate position between 0 ('The worst health you can imagine') and 100 ('The best health you can imagine'). FACT-M is a validated questionnaire that belongs to the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System.[25] The FACT-G (G for general) questionnaire (27 questions) is shared for all types of cancer. The FACT-M questionnaire contains 24 additional questions on symptoms specific to melanoma. The patient self-reports his/her HRQoL for the previous 7 days.

The questionnaires were completed in French or Dutch (translations provided and validated by EuroQol and FACIT). The questionnaires were anonymous, but a code allowed the patient's stage to be identified.

Data analysis

We converted the EQ-5D-5L states reported by each patient (e.g. 1,1,1,3,1) into a utility (in our example: 0·764). Following the EQ-5D-5L user guide,[26] we first used a crosswalk function to transform scores from the 5L scale to the 3L scale. Secondly, we transformed EQ-5D-3L scores to utilities according to a model based on social preference data obtained from a random sample of 2754 Belgian adults.[27] The resulting utility indicated, on a scale from 0 to 1, the HRQoL of the patient.

The utilities obtained by the EQ-5D method also reflect the comorbidities of the patients. To obtain the mean DWs (i.e. specific reduction in HRQoL due to the melanoma), we calculated the difference between the measured utility and the EQ-5D population norm (PN) for the same sex and age group for each patient.[28] As Belgian PNs were not available, we used PNs from the Netherlands (neighbouring country).[29]

Another common way to analyse the EQ-5D-5L questionnaire is to observe the proportion of patients reporting any problem in each dimension (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).[26]

The VAS scores correspond to the numbers chosen by the patients on the scale from 0 to 100.

The FACT-M scores were calculated according to the FACT-M scoring guidelines, version 4, provided by the FACIT after having registered the study. This score includes the FACT-G and the melanoma subscale (MS). In addition, a FACT-M Trial Outcome Index (TOI) includes a part of the FACT-G and the MS.

Statistical analyses

For all EQ-5D-5L and FACT-M derived scores, we calculated stage-specific and overall means and medians as measures of

central tendency; SD and interquartile ranges as measures of variability; and SEM with corresponding Wald-based 95% confidence intervals (CIs) as measures of uncertainty. For each score, we additionally calculated pairwise comparisons between each of the stages, using Holm's method to correct the individual P-values to reach a familywise significance level of 5%. For EQ-5D-5L, we also calculated the proportion of patients reporting any problem in each of the five dimensions. For each dimension, we used pairwise χ^2-tests to compare these proportions between each of the stages, using Holm's method to account for multiple comparisons. Finally, the correlations between the utilities, VAS scores, FACT-M scores and TOI scores were assessed by calculating Spearman's rank correlation coefficient for each pair of scores. Corresponding bootstrapped 95% CIs were obtained using function "spearman.ci" in R package RVAideMemoire version 0.9–35. All analyses were done treating the 395 questionnaires as independent observations. All calculations were performed in R version 3.0.1.[30]

Table 2 Population characteristics

Stage	n	Age (years), mean (range)	Sex ratio (male : female)
0/IA-T	68	51·7 (22–86)	0·67
0/IA-R	98	46·5 (18–87)	0·56
IB/II-T	33	54·5 (23–80)	0·83
IB/II-R	76	53·2 (22–80)	0·83
III-T	15	55·9 (25–83)	0·91
III-R	50	53·3 (19–86)	0·77
IV-T	41	61·4 (35–84)	1·0
IV-R	14	64·8 (22–84)	1·3
Total	395	52·6	0·74

T, treatment; R, remission.

Results

During the two inclusion periods, 501 patients were asked to participate in the study. Among them, 98 did not return the questionnaires. The majority (69%) of these patients were patients with stage 0–II melanoma in remission who had not seen the main investigator and had received less information about the aim of the study. The remaining nonparticipating patients had a similar distribution among stages as the participating patients. Participating and nonparticipating patients

Table 3 EuroQol results, applicable for given periods from the beginning of treatment

Stage	Periods	n	Mean	SD	SEM	95% CI	Median	IQR
Utilities								
0/IA-T	Month 1	68	0·687	0·192	0·023	0·642–0·733	0·678	0·578–0·811
0/IA-R	Months 2–24	98	0·809	0·179	0·018	0·773–0·844	0·798	0·723–1·000
IB/II-T	Months 1–2	33	0·579	0·272	0·047	0·486–0·671	0·665	0·295–0·798
IB/II-R	Months 3–24	76	0·802	0·166	0·019	0·764–0·839	0·798	0·703–1·000
III-T	Months 1–3	15	0·535	0·278	0·072	0·395–0·676	0·613	0·307–0·744
III-R	From Month 4	50	0·703	0·156	0·022	0·659–0·746	0·696	0·675–0·798
IV-T	From start of treatment	41	0·583	0·192	0·030	0·524–0·642	0·597	0·440–0·764
IV-R	From start of remission	14	0·796	0·167	0·045	0·708–0·883	0·722	0·675–1·000
Total		395	0·719	0·211	0·011	0·699–0·740	0·720	0·639–0·811
Disability weights								
0/IA-T	Month 1	68	0·232	0·167	0·020	0·193–0·272	0·228	0·109–0·323
0/IA-R	Month 2–24	98	0·127	0·147	0·015	0·098–0·156	0·112	0·000–0·188
IB/II-T	Month 1–2	33	0·335	0·257	0·045	0·247–0·422	0·245	0·112–0·582
IB/II-R	Month 3–24	76	0·133	0·132	0·015	0·103–0·163	0·120	0·000–0·205
III-T	Month 1–3	15	0·372	0·268	0·069	0·236–0·508	0·293	0·186–0·593
III-R	From Month 4	50	0·207	0·147	0·021	0·166–0·247	0·196	0·124–0·249
IV-T	From start of treatment	41	0·315	0·188	0·029	0·258–0·373	0·298	0·146–0·479
IV-R	From start of remission	14	0·136	0·122	0·033	0·072–0·200	0·168	0·000–0·242
Total		395	0·203	0·186	0·009	0·185–0·222	0·175	0·082–0·267
Visual analogue scale								
0/IA-T	Month 1	68	72·9	14·4	1·8	69·4–76·3	75·0	65·0–85·0
0/IA-R	Month 2–24	98	79·0	11·8	1·2	76·7–81·3	80·0	70·0–90·0
IB/II-T	Month 1–2	33	76·3	14·1	2·5	71·5–81·2	80·0	68·8–88·5
IB/II-R	Month 3–24	76	80·3	13·4	1·5	77·3–83·3	80·0	73·8–90·0
III-T	Month 1–3	15	68·2	18·1	4·8	58·7–77·7	72·5	62·5–78·8
III-R	From Month 4	50	76·6	15·2	2·1	72·4–80·8	80·0	70·0–90·0
IV-T	From start of treatment	41	63·6	17·7	2·8	58·2–69·1	65·0	53·8–75·0
IV-R	From start of remission	14	80·0	12·2	3·3	73·6–86·4	80·0	76·2–87·5
Total		395	75·7	14·9	0·8	74·3–77·2	80·0	70·0–88·0

CI, confidence interval; IQR, interquartile range; T, treatment; R, remission.

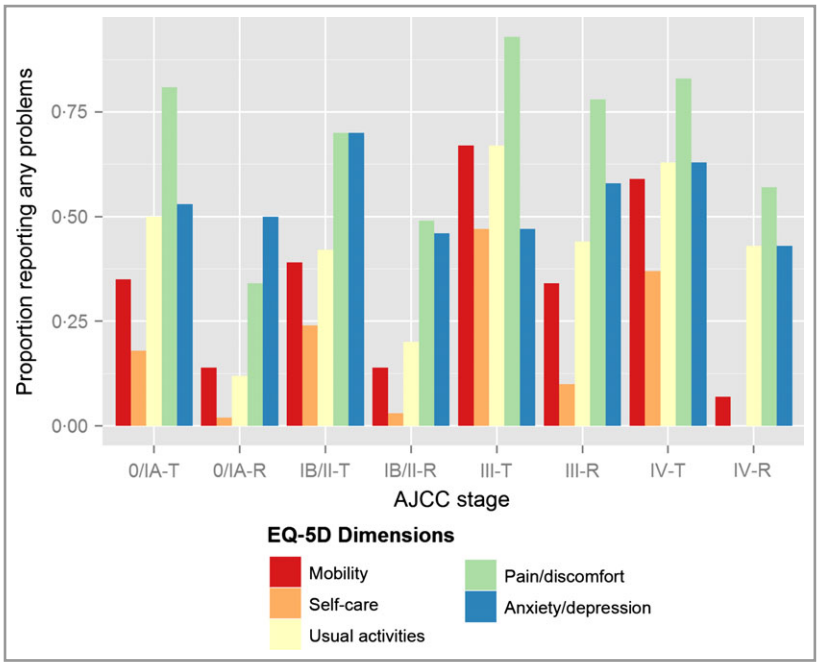

Fig 1. Proportion of patients reporting any problem in the EuroQol Five Dimensions Five Levels (EQ-5D-5L) questionnaire (in percentages). Differences are statistically significant (corrected $P < 0{\cdot}05$) between (i) patients with stage 0/IA melanoma in treatment vs. patients in remission, regarding their self-care, usual activities and pain/discomfort, (ii) patients with stage 0–II melanoma vs. stage III patients in remission regarding their usual activities (stage 0/IA vs. III) and their pain/discomfort (stages 0/IA or IB/II vs. III). R, remission; T, treatment.

were comparable in terms of mean age and sex ratio (results not shown). Eight questionnaire sets were incomplete. Finally, 395 questionnaire sets were available for inclusion in the study. Thirty-nine patients completed the same questionnaire set twice because they were seen in two different phases (treatment and follow-up) and/or stages during the inclusion period. Mean ages and sex ratios of the participating patients are presented in Table 2.

EuroQoL Five Dimensions Five Levels questionnaire results

Mean and median utilities and DWs are presented in Table 3. Within each of the four stages, patients in treatment had a lower mean utility and a higher mean DW than patients in remission. This difference was significant (corrected $P < 0{\cdot}05$) for stages 0–IA, IB–II and IV. The difference was not significant in stage III patients, probably because of the small number of stage III patients in treatment within our sample (15 patients). When we compared utilities and DWs patients in treatment in one stage with those of the following stages, there was no statistically significant difference. In the same way, when we compared patients in remission in one stage with those of the following stages, we could observe a statistically significant difference between stages 0–IA or IB–II and patients with stage III melanoma (corrected $P < 0{\cdot}05$). The difference between mean utilities in male patients (0·747) and female patients (0·699) was statistically significant ($P = 0{\cdot}03$) but the difference between the mean DWs in male patients (0·175) and female patients (0·191) was not.

We observed the proportion of patients reporting any kind of problem in each of the five dimensions (Fig. 1). Pain/discomfort was the most common problem, reported by 62% of the patients. Anxiety/depression was reported by 54% of the patients, without any significant difference between any of the stages or treatment/remission phases.

Visual analogue scale results

The VAS results (Table 3) showed only statistically significant differences between the patients with stage IV melanoma in treatment vs. remission, and among patients in remission between stage 0–IA vs. III.

Functional Assessment of Cancer Therapy Melanoma questionnaire results

The FACT-M results (Table 4) did not show any statistical difference between any of the stages or treatment/remission phases. Nevertheless, the FACT-M TOI results revealed statistically significant differences in each stage when comparing treatment and remission phases.

All correlations between the FACT-derived scores and the EQ-derived scores were positive and statistically significantly different from zero (Table 5).

We studied the 84 patients who had filled in the EQ-5D-5L with (1,1,1,1,1), which led to a utility of 1 (perfect HRQoL). Seventy-two were in stage 0–II, 12 were in stage III or IV. Among those patients who had chosen '1' (no problem) for the anxiety/depression item in the EQ-5D-5L, the FACT-M results show that 46 of 84 were not completely satisfied with how they were coping with their illness, and 12 of 84 were not satisfied at all, while 28 of 84 were somewhat, quite a bit or very much worried that their condition would get worse. These results are unrelated to the stage and the treatment/remission phase.

Table 4 Functional assessment of cancer therapy (FACT) results

Stage		n	Mean	SD	SEM	95% CI	Median	IQR
FACT-M (score range 0–172)								
0/IA-T	Month 1	68	131·0	23·6	2·9	125·3–136·7	132·0	114·0–149·5
0/IA-R	Month 2–24	98	141·3	18·8	1·9	137·6–145·1	146·0	134·5–154·5
IB/II-T	Month 1–2	33	130·3	22·0	4·0	122·5–138·0	134·0	120·0–145·2
IB/II-R	Month 3–24	76	142·0	19·7	2·3	137·6–146·4	145·0	131·5–155·6
III-T	Month 1–3	15	117·1	26·6	6·9	103·6–130·5	115·0	99·0–141·3
III-R	From Month 4	50	136·8	18·8	2·6	131·6–141·9	136·9	124·2–151·0
IV-T	From start of treatment	41	117·9	27·4	4·3	109·4–126·4	115·2	101·3–139·2
IV-R	From start of treatment	14	141·5	14·1	3·8	134·1–148·9	139·2	134·8–151·0
Total		395	134·8	22·6	1·1	132·6–137·1	139·0	120·0–152·0
FACT-M TOI (score range 0–120)								
0/IA-T	Month 1	68	93·1	17·9	2·2	88·8–97·4	96·0	84·5–106·5
0/IA-R	Month 2–24	98	102·5	13·8	1·4	99·7–105·3	105·7	98·0–112·0
IB/II-T	Month 1–2	33	91·0	18·5	3·3	84·5–97·5	94·0	83·4–107·0
IB/II-R	Month 3–24	76	101·9	13·5	1·5	98·8–104·9	105·0	96·5–111·1
III-T	Month 1–3	15	79·6	20·5	5·3	69·2–90·0	81·0	61·0–99·0
III-R	From Month 4	50	98·2	13·7	1·9	94·5–101·9	101·2	87·0–109·2
IV-T	From start of treatment	41	81·7	20·2	3·2	75·4–88·0	79·2	73·0–95·0
IV-R	From start of treatment	14	99·4	9·4	2·5	94·5–104·4	97·5	94·2–105·5
Total		395	96·2	17·3	0·9	94·5–97·9	100·0	86·0–110·0

CI, confidence interval; IQR, interquartile range; R, remission; T, treatment. FACT-Melanoma [FACT-M; FACT-General (FACT-G) + melanoma subscale] and FACT-M Trial Outcome Index (TOI; physical and functional well-being subscales from FACT-G + melanoma subscale). Health-related quality-of-life increases in line with the score.

Table 5 Spearman's rank correlation coefficients and corresponding bootstrapped 95% confidence intervals for each pairwise combination of the four used methods used

	FACT-M	TOI	EQ-5D-5L
TOI	0·96 (0·94–0·96)	–	–
EQ-5D-5L	0·75 (0·70–0·79)	0·76 (0·71–0·81)	–
VAS	0·64 (0·57–0·71)	0·67 (0·60–0·73)	0·57 (0·48–0·64)

Functional Assessment of Cancer Therapy Melanoma (FACT-M), FACT-M Trial Outcome Index (TOI), utility obtained with EuroQol Five Dimensions Five Levels (EQ-5D-5L), and visual analogue scale (VAS).

Discussion

Using 395 EQ-5D-5L questionnaires in Belgian patients with melanoma, the present study provides mean utilities and DWs regarding patients with melanoma who were categorized into eight groups using a four-stage grouping based on the 2009 AJCC classification (0–IA, IB–II, III and IV), with each stage being subdivided into treatment and remission phases. Within each of the four stages, patients in treatment had a lower mean utility and a higher mean DW than patients in remission. By comparing patients in one stage with those in the following stage(s), there was no significant difference for the patients in treatment but we found a statistically significant difference between stages 0–IA or IB–II and patients with stage III melanoma in remission.

It may seem surprising not to find any statistically significant difference in HRQoL between the patients in the different treatment stages. As an example, one would expect that the HRQoL of a patient undergoing a wide excision and an elective node dissection would be lower than the HRQoL of a patient who undergoes a simple wide excision. Nevertheless, this is not reflected in the values of the utilities and DW. One should not forget that the utilities and DWs of the treatment stages are applicable for a specific duration given in months. Based on expert opinions, we assumed the following durations: 1, 2 and 3 months for stages 0–IA, IB–II and III, respectively and more than 10 months for stage IV according to the most recent studies.[31,32] In our example, a simple linear application of the same utility of 0·6 in both patients over the entire stage duration will result in 0·05 QALY ($0{\cdot}6/12 \times 1$) in the case of a patient with stage IA melanoma and 0·15 QALY ($0{\cdot}6/12 \times 3$) in the case of a patient with stage III melanoma. In other words, a similar utility has cumulative consequences in QALY and DALY calculations, proportional to the assumed duration of the treatments. Note that the validity of such a linear imputation over the entire duration is only rarely challenged in current-day applied CEAs.[33]

We found a good HRQoL in patients with stage 0–II melanoma in remission for < 2 years (DWs around 0·1). These results are in line with previous studies conducted using other instruments, studying patients with localized melanoma either from 6 months to 10 years[34] or 2 years[22] after the diagnosis. They concluded that the HRQoL was comparable with that of the general population. The questionnaires were perhaps not sensitive enough to pick up some of the difficulties experienced

by these patients: some patients with stage 0–II melanoma in remission for several years still experience problems with sun protection, with obtaining health insurance, and coping with the illness.[34] Nevertheless, half of the patients reported 'a change for the better in their attitude towards life'.[22] We can, therefore, reasonably assume that positive and negative consequences of an 'old' localized melanoma lead together to a mean HRQoL as good as the mean HRQoL of the general population.

Several studies found a more impaired HRQoL in women than in men.[2,34] In our study, utilities were also significantly lower in women than in men. Nevertheless, the difference became insignificant in terms of DWs. The explanation is probably linked to the EQ-5D population norms, where women have worse HRQoL in all age groups in the Dutch sample we used. General population health status was studied in two publications in six and three European countries, respectively. More problems in four of the five EQ-5D dimensions were associated with female respondents in the first study.[35] Female patients had lower EQ-5D lower scores in the second study.[36] We must conclude that there is a probable bias concerning the utilities we provided for women. Nevertheless, this problem is linked to the methodology itself and possibly occurred in other published HRQoL studies that included both male and female respondents.

Compared with patients with stage 0–II melanoma in remission, we found a significantly lower mean HRQoL in patients with stage III melanoma in follow-up, while the patients were studied over a much longer remission duration. This result is consistent with other studies.[37,38]

It is surprising to observe the relatively good HRQoL of patients with stage IV melanoma in remission, similar to patients with stage 0–II melanoma in remission. Coping with the illness is probably the explanation for this observation. In quality-of-life research, this phenomenon is described as 'response shift'.[39]

Another interesting observation was the high frequency of slight-to-severe anxiety/depression, which was reported by 54% of the patients, without any significant difference between the stages. This symptom was reported by significantly fewer patients among the 1274 Belgians from the general population (from 16·9% for the 18–29-year age group, to 33·3% for the ≥ 80-year age group).[40] These results are in accordance with the literature: two concomitant systematic reviews of HRQoL in patients with melanoma concluded that one-third of patients with melanoma reported significant levels of distress.[1,2] In addition, our detailed analysis of the FACT-M results in patients with the maximum EQ-5D-5L score highlighted: (i) difficulties in coping with the illness, and (ii) worries about a worsening of the cancer in more than a half and one-third of these patients, respectively. These results were consistent across all the melanoma stages. We conclude that there is a potential insensitivity in the EQ-5D-5L questionnaire (anxiety/depression dimension) when used for patients with melanoma. This possible bias should be taken into consideration in CEAs, especially if they analyse an intervention on anxiety/depression in patients with melanoma.

Assuming that HRQoL is more impaired in a surgical treatment phase than in the corresponding remission phase, and that sequelae of the surgical treatments increase from stage 0–IA to stage III, we observed that EQ-5D-5L was more sensitive than VAS, FACT-M and FACT-M TOI, and that FACT-M TOI was more sensitive than FACT-M. A mapping of FACT-M scores to EQ-5D utilities found an R^2 equal to 0·499 (i.e. a Pearson correlation coefficient of 0·706), which is in accordance with our results (Spearman correlation coefficient of 0·75).[41]

Our study has some limitations. Firstly, it is a single-institution and single-country study. Nevertheless, we think that our results can be extrapolated, up to a certain point, to other Western countries. This extrapolation is supported by the following elements: (i) important correlations were observed between self-reported health problems on each EQ-5D dimension and gross domestic product (GDP) per capita.[40] Belgian GDP is, on average, closer to other Western countries than to many other countries in the world; (ii) available treatments and follow-up of melanoma in Belgium are also more similar to those used in other Western countries than those used in some other parts of the world.[42] Nevertheless, studies comparing self-reported health status using EQ-5D in different European countries are controversial.[35,36] Our results should therefore be used with caution in other (Western) countries. Secondly, we did not measure the HRQoL from the discovery of the suspicious lesion until the treatment, which is a possible important distress period.[43] Thirdly, information on the nature of patient comorbidities was not collected. Overall, physical and psychological health was found to be an important predictor of HRQoL impairment in patients with melanoma.[37] Ideally, our results should be confirmed by a larger international study, including more patients and additional information such as comorbidities. Nevertheless, the present study is based on a larger sample of patients compared with previous studies, which provided utilities and is more up to date regarding DWs. Our results are in line with many studies conducted with nongeneric instruments, which were therefore of little value for QALY and DALY calculations. We trust that our data will further contribute to melanoma CEAs and burden assessments.

References

1 Cornish D, Holterhues C, van de Poll-Franse LV *et al.* A systematic review of health-related quality of life in cutaneous melanoma. *Ann Oncol* 2009; **20** (Suppl. 6):vi51–8.

2 Kasparian NA, McLoone JK, Butow PN. Psychological responses and coping strategies among patients with malignant melanoma: a systematic review of the literature. *Arch Dermatol* 2009; **145**:1415–27.

3 Gibbons E, Casañas i Comabella C, Fitzpatrick R. A structured review of patient-reported outcome measures for patients with skin cancer, 2013. *Br J Dermatol* 2013; **168**:1176–86.

4 Cormier JN, Ross MI, Gershenwald JE *et al.* Prospective assessment of the reliability, validity, and sensitivity to change of the Functional Assessment of Cancer Therapy-Melanoma questionnaire. *Cancer* 2008; **112**:2249–57.

5 Bendeck SE, Hadley JC, Bonaccorsi P *et al.* Can melanoma patients predict the quality of life impact of an alternate melanoma stage? Presented at the 26th *Annual Meeting of the Society for*

Medical Decision Making, Atlanta, GA, U.S.A., 17–20 October 2004; P1530.
6 Bendeck SE, Hadley JC, Bonaccorsi P *et al.* Quality of life impact by melanoma as measured by utilities. Presented at the 26th Annual Meeting of the Society for Medical Decision Making, Atlanta, GA, U.S.A., 17–20 October 2004; P1524.
7 Hirst NG, Gordon LG, Scuffham PA, Green AC. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. *Value Health* 2012; **15**:261–8.
8 Losina E, Walensky RP, Geller A *et al.* Visual screening for malignant melanoma: a cost-effectiveness analysis. *Arch Dermatol* 2007; **143**:21–8.
9 Morton RL, Howard K, Thompson JF. The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma. *Ann Surg Oncol* 2009; **16**:929–40.
10 Wilson EC, Emery JD, Kinmonth AL *et al.* The cost-effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model. *Value Health* 2013; **16**:356–66.
11 King SM, Bonaccorsi P, Bendeck S *et al.* Melanoma quality of life: pilot study using utility measurements. *Arch Dermatol* 2011; **147**:353–4.
12 Brennan DS, Spencer AJ. Disability weights for the burden of oral disease in South Australia. *Popul Health Metr* 2004; **2**:7.
13 Essink-Bot ML, Pereira J, Packer C *et al.* Cross-national comparability of burden of disease estimates: the European Disability Weights Project. *Bull World Health Organ* 2002; **80**:644–52.
14 Haagsma JA, Polinder S, van Beeck EF *et al.* Alternative approaches to derive disability weights in injuries: do they make a difference? *Qual Life Res* 2009; **18**:657–65.
15 Mathers CD, Vos ET, Stevenson CE, Begg SJ. The burden of disease and injury in Australia. *Bull World Health Organ* 2001; **79**:1076–84.
16 Stouthard M, Essink-Bot M-L, Bonsel G *et al. Disability Weights for Diseases in the Netherlands*. Amsterdam: Inst. Sociale Geneeskunde, 1997.
17 Holterhues C, Hollestein LM, Nijsten T *et al.* Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991. *Br J Dermatol* 2013; **169**:389–97.
18 Herdman M, Gudex C, Lloyd A *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**:1727–36.
19 Balch CM, Gershenwald JE, Soong SJ *et al.* Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; **27**:6199–206.
20 Bergenmar M, Mansson-Brahme E, Hansson J, Brandberg Y. Surgical resection margins do not influence health related quality of life or emotional distress in patients with cutaneous melanoma: results of a prospective randomised trial. *Scand J Plast Reconstr Surg Hand Surg* 2010; **44**:146–55.
21 Tsuchiya A, Dolan P. The QALY model and individual preferences for health states and health profiles over time: a systematic review of the literature. *Med Decis Making* 2005; **25**:460–7.
22 Schlesinger-Raab A, Schubert-Fritschle G, Hein R *et al.* Quality of life in localised malignant melanoma. *Ann Oncol* 2010; **21**:2428–35.
23 Eggermont AM, Suciu S, Testori A *et al.* Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. *Eur J Cancer* 2012; **48**:218–25.
24 Janssen MF, Pickard AS, Golicki D *et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013; **22**:1717–27.
25 FACIT. Functional Assessment of Chronic Illness Therapy. Available at: http://www.facit.org/FACITOrg/Questionnaires (last accessed on 11 November 2014).
26 EuroQol. EQ-5D-5L user guide. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf (last accessed on 11 November 2014).
27 Cleemput I. A social preference valuations set for EQ-5D health states in Flanders, Belgium. *Eur J Health Econ* 2010; **11**:205–13.
28 Haagsma JA, van Beeck EF, Polinder S *et al.* The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. *Popul Health Metr* 2011; **9**:10.
29 Hoeymans N, van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. *Qual Life Res* 2005; **14**:655–63.
30 R Foundation for Statistical Computing. R: A language and environment for statistical computing. Available at: http://www.r-project.org/ (last accessed on 11 November 2013).
31 Robert C, Thomas L, Bondarenko I *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364**:2517–26.
32 Sosman JA, Kim KB, Schuchter L *et al.* Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012; **366**:707–14.
33 Luyten J, Marais C, Hens N *et al.* Imputing QALYs from single time point health state descriptions on the EQ-5D and the SF-6D: a comparison of methods for hepatitis a patients. *Value Health* 2011; **14**:282–90.
34 Holterhues C, Cornish D, van de Poll-Franse LV *et al.* Impact of melanoma on patients' lives among 562 survivors: a Dutch population-based study. *Arch Dermatol* 2011; **147**:177–85.
35 König HH, Bernert S, Angermeyer MC *et al.* Comparison of population health status in six european countries: results of a representative survey using the EQ-5D questionnaire. *Med Care* 2009; **47**:255–61.
36 Bernert S, Fernandez A, Haro JM *et al.* Comparison of different valuation methods for population health status measured by the EQ-5D in three European countries. *Value Health* 2009; **12**:750–8.
37 Schubert-Fritschle G, Schlesinger-Raab A, Hein R *et al.* Quality of life and comorbidity in localized malignant melanoma: results of a German population-based cohort study. *Int J Dermatol* 2013; **52**:693–704.
38 de Vries M, Hoekstra HJ, Hoekstra-Weebers JE. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. *Ann Surg Oncol* 2009; **16**:2840–7.
39 Sprangers MA, Schwartz CE. The challenge of response shift for quality-of-life-based clinical oncology research. *Ann Oncol* 1999; **10**:747–9.
40 Szende A, Williams A. Measuring Self-Reported Population Health: An International Perspective based on EQ-5D. Available at: http://www.euroqol.org/fileadmin/user005Fupload/Documenten/PDF/Books/Measuring_Self-Reported_Population_Health_-_An_International_Perspective_based_on_EQ-5D.pdf (last accessed on 11 November 2014).
41 Askew RL, Swartz RJ, Xing Y *et al.* Mapping FACT-melanoma quality-of-life scores to EQ-5D health utility weights. *Value Health* 2011; **14**:900–6.
42 Fong ZV, Tanabe KK. Comparison of melanoma guidelines in the U.S.A., Canada, Europe, Australia and New Zealand: a critical appraisal and comprehensive review. *Br J Dermatol* 2014; **170**:20–30.
43 Burdon-Jones D, Thomas P, Baker R. Quality of life issues in non-metastatic skin cancer. *Br J Dermatol* 2010; **162**:147–51.

