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Original Research

Melanoma burden by melanoma stage: Assessment through a disease transition model

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KEYWORDS
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Abstract ***Background:*** The total burden of melanoma has already been studied but little is known about the distribution of this burden amongst localised, node metastatic and distant metastatic stages.
Methods: Disability-adjusted life years (DALY) assesses disease burden, being the sum of years of life with disability (YLD) and years of life lost (YLL). A melanoma disease model was developed in order to predict the evolution of patients from diagnosis until death. The

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model was applied to a large cohort of 8016 melanoma patients recorded by the Belgian Cancer Registry for incidence years 2009–2011. DALYs were calculated for each American Joint Committee on Cancer stage, considering stage at diagnosis on the one hand and time spent in localised, node metastatic and visceral metastatic stages on the other. Probabilistic sensitivity analyses and scenario analyses were performed to explore uncertainty.

Findings: Our analyses resulted in 3.67 DALYs per melanoma, 90.81 per 100,000 inhabitants, or 32.67 per death due to melanoma. The total YLL accounted for 80.4% of the total DALY. Stages I, II, III and IV patients at diagnosis generated, respectively, 27.8%, 32.7%, 26.2% and 13.3% of the total YLL. For the time spent in each stage, localised melanomas, node metastatic melanomas, and distant metastatic accounted, respectively, for 34.8%, 52.6% and 12.6% of the total YLD. Parametric uncertainty was very limited, but the influence of using pre-2010 Global Burden of Disease approaches was substantial.

Interpretation: The total DALY for melanoma was consistent with the previous studies. Our results in terms of proportions of DALY/YLL/YLD per stage could be extrapolated to other high-income countries. YLDs generated by localised melanoma which will never metastasize were inferior to YLLs resulting from stage IA melanomas. This result supports the hypothesis that efforts for an earlier diagnosis of melanoma are important.

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1. Introduction

In most Western countries, the melanoma incidence is still increasing, despite primary prevention efforts. This increase primarily correlates with an increased diagnosis of (very) early melanomas, probably due to secondary prevention efforts. Melanoma-related mortality is either stable or still increasing, yet much slower than the incidence [1]. This discrepancy is reported to be related to overdiagnosis [2–4] and/or to the fact that most melanoma deaths are due to fast-growing melanomas, the incidence of the latter being stable because rarely identified during screenings [5,6]. Due to its relatively low mean age at diagnosis, melanoma ranks among the most devastating adult cancers in terms of years of life lost (YLL) per death [7,8]. Nevertheless, the emergence of new, yet expensive treatments for metastatic melanoma kindles hope for a decreased mortality in the coming decades, despite being associated with longer disease durations.

This epidemiological and economical context asks for a quantification of the burden of melanoma, allowing to assess the disease impact on society. Most studies on melanoma screening or treatments chose survival as the main end-point, with no consideration of health-related quality of life (HRQoL), even though it is a non-negligible factor [9–11]. The disability-adjusted life years (DALY), a measure of disease burden, takes into account not only the YLL due to disease but also the years of life with disability (YLD). DALY assessments help to compare the burden of any diseases between [12,13] or within [14] countries, as well as over time [15].

The total burden of melanoma has already been studied [12,13,15–17]. Nevertheless, the methods previously used have never assessed the respective weights of the different melanoma stages. In this paper, we used DALY to assess the burden of the different melanoma stages, deriving our results from the melanoma incidence in Belgium in years 2009–2011. A new disease model was constructed to assess burden of melanoma in terms of localised, node, and distant metastatic stages. This division of the burden of melanoma may assist in setting priorities for healthcare resource allocations, especially when choices must be made between screening and metastatic patient treatments.

2. Materials and methods

2.1. Population

The Belgian Cancer Registry [18] records all new melanoma cases through oncological care programs and pathology laboratories. The World Health Organisation considers these Belgian incidence measurements of high quality [19]. At the time of this study, the most recent available data were until incidence year 2011, but to provide a more rigorous representation, we included the 2009–2011 incidence data. In the case of multiple primary melanomas, the melanomas are encoded as different lesions if topography and laterality are different. Stages are encoded according to the "tumour-node-metastasis" (TNM) classification [20]. Using the seventh American Joint Committee on Cancer (AJCC) staging [21], we expressed the TNM information as AJCC stages. Patients with missing or incomplete data for TNM categories were re-classified according to the proportions of patients in the possible stages.

2.2. Disability weights

The DALYs for melanomas are the sum of YLLs due to melanomas and the melanoma-related YLDs. The YLDs were obtained by multiplying the number of person-years lived in various melanoma "states" by the disability weight (DW) associated with each state, a number between 0 (perfect health or no melanoma-related disability) and 1 (death). We used the recently published DWs for melanoma [22], by AJCC stage, each divided into treatment and remission phases. Each DW was applicable for a given period of treatment or remission. According to the previous studies [23,24], stage 0–II patients were assumed to have an HRQoL equal to that of the normal population, from 2 years following diagnosis until recurrence or death. The DWs used are presented in Table 1.

2.3. Disease model and transition probabilities

Fig. 1 shows the new disease model we propose for melanoma. This model is inspired by "Markov models" used in cost-effectiveness analyses, but allows some additional features. All melanoma patients from the 2009–2011 Belgian Cancer Registry cohort were set to start at one of the diagnosis states and entered into the model for a certain number of cycles until death. The duration of a cycle was set to 1 year. During each cycle, every patient can either stay in the same state or move to another state depending on so-called 'transition probabilities'. All transition probabilities were derived on a yearly basis and transition probabilities to the next cycle states were conditional on the time spent in the actual cycle state. We estimated the transition probabilities of recurrences from stages I, II or III to stage III using the data presented in Leiter et al. [25]. Transition probabilities from stage III to recurrence to stage IV were derived from the observation arm data of the European Organisation for Research and Treatment of Cancer (EORTC) 18991 trial [26]. For each transition from one stage to the other, the transition probabilities were estimated from the available data by fitting a piecewise yearly constant hazard survival model for time to transition to the next stage. The transition probabilities were computed from the estimated value of the hazards for the first 10 years and assumed to be zero thereafter. Since neither databases allowed separating of stages IIIB and IIIC, these were pooled. The transition probabilities from stage IV to death from melanoma were based on the last available results of ipilimumab in these patients [27], and yearly transition probabilities were derived directly from the survival estimates at years 1 to 4 available in the publication. Patients remained in the model until death due to melanoma or until they reached their life expectancy (determined at age of diagnosis), the latter information was obtained using the Belgian life tables [28]. For patients who died from melanoma, the YLLs were calculated according to their normative life expectancy at the time of death as available from the age-specific standard life tables created for the Global Burden of Disease (GBD) 2010 study [29].

2.4. Data and model assumptions

Although our model aimed to mimic reality as much as possible, some simplifying assumptions had to be made. Regarding the data, the following assumptions were made: (a) all pT1a-stage patients without suspicious nodal or distant metastases on clinical examination were classified as IA, even if they underwent neither sentinel node biopsy (SNB) nor extensive staging; (b) all pT1b to pT4b-stage patients without clinically palpable nodes underwent SNB and staging by computed tomography (CT) or positron emission tomography CT; (c) patients diagnosed with multiple primary melanoma in 2009–2011 were considered as separate patients for each of their melanoma except if the latter occur in a same topography and laterality; and (d) transition probabilities from stage IV to death assumed that all stage IV patients received ipilimumab. Since age and gender

Table 1
Number of patients (Belgium, 2009–2011), DW.

	Men	Women	Total	DW treatment (95% CI) (treatment duration)	DW remission (95% CI) (remission duration)
Stage 0 (*in situ*)	717	1055	1772	0.232 (0.193–0.272) (1st month)	0.127 (0.098–0.156) (2nd to 24th month)
Stage IA	888	1544	2432		
Stage IB	414	583	997	0.335 (0.247–0.422) (2 first months)	0.133 (0.103–0.163) (3rd to 24th month)
Stage IIA	217	284	501		
Stage IIB	183	221	404		
Stage IIC	104	90	194		
Stage IIIA	43	43	86	0.372 (0.236–0.508) (3 first months)	0.207 (0.166–0.247) (from 4th month to death or to recurrence to stage IV)
Stage IIIB	83	77	160		
Stage IIIC	68	55	123		
Stage IV	83	50	133	0.315 (0.258–0.373) (real period of treatment)	0.136 (0.072–0.200) (real period of remission)
Unknown stage	478	736	1214		
Total	3278	4738	8016		

DW: disability weight, CI: confidence interval.

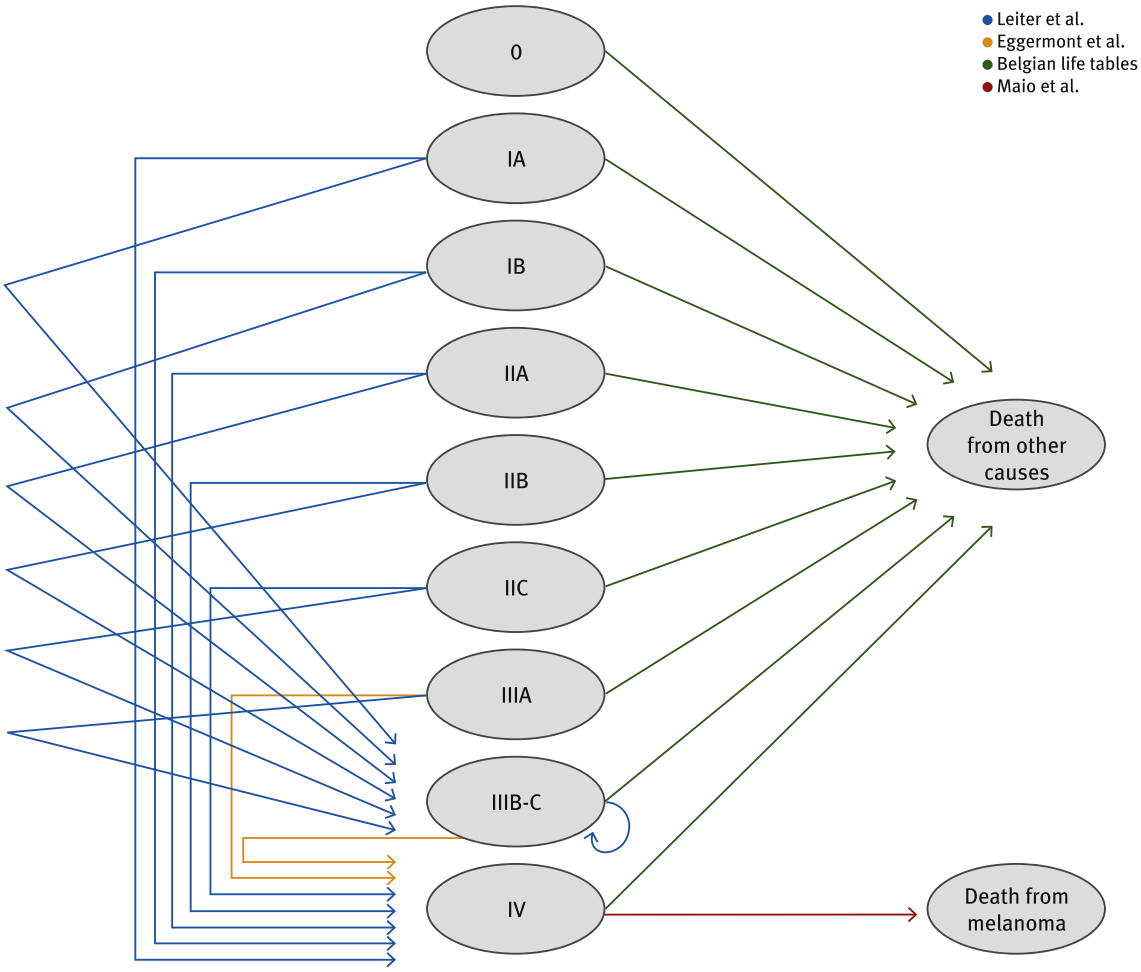

Fig. 1. Melanoma disease model.

distributions by AJCC stage were not readily available from the Belgian Cancer Registry data, this was done only for stage 0 and IV patients, while the distribution observed in the Leiter data was used for stage I–III patients. With regards to the model itself, it was built upon the following assumptions: (a) transition probabilities were assumed to be the same for both genders and all ages (but life expectancies were based on age and gender); (b) for patients transitioning over multiple stages during a single year, only their latest transition was used to estimate the transition probabilities to the latest stage; (c) strictly local recurrences were not included owing to their rarity, and in-transit metastasis were included as stage IIIB-C; (d) stage IIIB-C patients were actually allowed to recur back to stage IIIB-C only a maximum of two times; (e) we assumed no melanoma-related deaths during stages 0 to III; and (f) transition to the next stage was only assumed to occur during the first 10 years spent in the current stage.

2.5. DALY calculations

Firstly, we considered the AJCC stage at diagnosis and calculated the DALY of each stage cohort from diagnosis to death. Secondly, we considered each AJCC stage as a phase between diagnosis of this stage and recurrence or death, calculating the YLD of each phase, irrespective of patient status before and after this phase. We also explored methodological uncertainty through scenario analyses (SAs). In a first SA, *in situ* melanomas were removed from the database. In a second SA, the pre-2010 GBD approach was applied, i.e. a 3% discount rate, age weighting and a previous version of the standard life tables [30]. A third SA combined the first and the second SA, excluding *in situ* melanomas and applying the pre-2010 GBD approach. All computations were based on the patients from the 2009–2011 Belgian Cancer Registry cohort, and averaged out to represent the average annual situation in this period.

2.6. Probabilistic sensitivity analysis

To jointly investigate the impact of the uncertainty in the different model parameters, a probabilistic sensitivity analysis (PSA) was conducted. Uncertainty was considered for transition probabilities, DWs, and the number and distribution of patients at diagnosis states. The DALY computation was repeated 1000 times

Table 2
YLD, YLL, and DALY according to the stage at diagnosis.

	Number of patients[a]	YLD/year							YLL/year			DALY/year				
		Initial treatment	Follow-up without recurrences	Treatment of reccurences to stage IIIB-C	Follow-up after reccurences to stage IIIB-C	Treatment and follow-up of reccurences to stage IV	Total	Per melanoma	Per death	Total	Per melanoma	Per death	Men	Women	Total	Per melanoma	Per death
Stage 0	2088	13	169	NA[b]	NA[b]	NA[b]	183	0.26	NA[b]	NA[b]	NA[b]	NA[b]	74	109	183	0.26	NA[b]
Stage IA	2866	18	232	6	122	26	404	0.42	11.80	1003	1.05	29.34	509	898	1407	1.47	41.14
Stage IB	1175	22	94	7	143	31	297	0.76	7.02	1188	3.03	28.05	611	875	1486	3.79	35.07
Stage IIA	590	11	46	7	135	29	228	1.16	5.66	1031	5.24	25.60	540	720	1260	6.41	31.26
Stage IIB	476	9	35	7	129	30	210	1.32	5.01	1025	6.46	24.43	554	681	1235	7.78	29.45
Stage IIC	229	4	16	4	61	16	102	1.34	4.41	522	6.83	22.58	332	292	624	8.17	26.99
Stage IIIA	101	3	77	2	40	11	133	3.95	9.26	412	12.24	28.71	268	276	545	16.19	37.97
Stage IIIB-C	334	10	127	7	125	45	315	2.83	5.10	1652	14.83	26.76	1040	926	1966	17.66	31.86
Stage IV	157	16	38	0	0	0	55	1.05	1.30	1048	20.03	24.84	731	373	1103	21.08	26.14
Total	8016	106	834	40	755	188	1927	0.72	6.42	7882	2.95	26.26	4658	5150	9808	3.67	32.67

DALY: disability-adjusted life year; YLD: years lived with disability; YLL: years of life lost; NA: not applicable.
[a] Unknown stages are re-allocated proportionally – 3-year Belgian Cancer Registry cohort.
[b] Not applicable – no recurrences to stage III nor death for melanoma amongst patients with stage 0 at diagnosis.

considering for each repetition that the values of these parameters were randomly drawn from a probability distribution reflecting their uncertainty. The probability distributions used were gamma for the transition probabilities (with parameter values determined based on the confidence interval of the estimated hazard), beta for DWs (idem), and Poisson for the total number of patients with a Dirichlet distribution for the distribution amongst stages at diagnosis. The results obtained over the 1000 replications were used to derive an average PSA value (PSA-avg) and a 95% PSA-credible interval (PSA-CI) for our main results.

3. Results

The distribution of melanoma patients from the Belgian Cancer Registry in the different stages is presented in Table 1. In 2009, 2010, and 2011, a total of, respectively, 2442, 2740, and 2834 patients were diagnosed with melanoma. There were 3278 men and 4738 women. In total, 1214 patients had a melanoma with a completely unknown stage. In addition, the stage was partially unknown for 942 patients. In Table 1, the latter patients have already been re-allocated according to the proportions of patients in the possible stages. As an example, 793 patients were known to be in stage I and were distributed into stages IA and IB according to the proportions of patients in these stages.

The results for the burden of melanoma are presented in Tables 2 and 3, and the results from the PSA are in Table 4. The total annual DALY in Belgium for the period 2009–2011 was 9808 (PSA-avg: 98.03, 95% PSA-CI: 91.73–10.37). Women generated 53% of the total DALY. The total DALY was 3.67 per melanoma case (PSA-avg: 3.67, 95% PSA-CI: 3.46–3.87) or 90.81 per 100,000 inhabitants (based on a population of 10.8 million in Belgium) (PSA-avg: 90.77, 95% PSA-CI: 84.93–96.02) or 32.67 per death from melanoma (PSA-avg: 32.70, 95% PSA-CI: 31.80–33.74). When considering the stage at initial diagnosis (Table 2), the DALY per melanoma increased from stage 0 (0.26 per melanoma) to stage IV (21.08 per melanoma). The total annual YLL was 7882, accounting for 80.4% of the total DALY. Stage I patients at diagnosis generated 2191 (27.8%) annual YLL (1003 and 1188 from stages IA and IB, respectively, at diagnosis). Stage II generated 2578 (32.7%) annual YLL. Annual YLL values of 2064 (26.2%) and 1048 (13.3%) were obtained for stages III and IV, respectively, at diagnosis. The total annual YLD was 1927, 19.6% of the total DALY. For the time spent in each stage (Table 3), localised melanomas accounted for 183, 366, and 121 YLDs for stages 0, I, and II, respectively. Localised melanomas represented 670 YLDs, 34.8% of the total melanoma-related morbidity. Node metastatic melanomas accounted for 1014 (52.6%) and distant metastatic for 243 (12.6%) of the total YLD. Table 4

Table 3
DALY/year according to the time spent by the patients in each stage and univariate SAs.

	Men	Women	Total	Men per 100,000	Women per 100,000	Total per 100,000
YLD from stage 0	74	109	183	1.40	1.98	1.70
YLD from stage I	139	227	366	2.63	4.12	3.39
YLD from stage II	55	66	121	1.04	1.19	1.12
YLD from stage III	437	577	1014	8.24	10.49	9.39
YLD from stage IV	119	125	243	2.24	2.26	2.25
Total YLD	824	1102	1927	15.55	20.04	17.84
YLL	3834	4047	7882	72.34	73.59	72.98
Total DALY	4658	5150	9808	87.89	93.64	90.81
Total DALY 1st SA	4584	5041	9625	86.49	91.66	89.12
Total DALY 2nd SA	2246	2612	4858	42.38	47.49	44.98
Total DALY 3rd SA	2174	2506	4680	41.02	45.56	43.33

DALY: disability-adjusted life year; SA: scenario analysis; YLD: years lived with disability; YLL: years of life lost.
1st SA : *in situ* melanoma excluded.
2nd SA: pre-2010 Global Burden of Disease approach.
3rd SA: *in situ* melanoma excluded and pre-2010 Global Burden of Disease approach.

indicates that parametric uncertainty has only a small impact on the results.

When removing *in situ* melanoma (Tables 3 and 4, first SA), the total DALY was reduced by 1.9%. When calculating the burden of melanoma according to the pre-2010 GBD approach (second SA), the total DALY became 44.98 (PSA-avg: 44.94, 95% PSA-CI: 42.10–47.77), i.e. a reduction of 50%, mainly due to applying the discount rate and age weighting. When removing *in situ* melanomas, and calculating the burden of melanoma according to the pre-2010 GBD approach, the total DALY became 43.33 (PSA-avg: 43.28, 95% PSA-CI: 40.62–45.94).

Table 4
Probabilistic sensitivity analysis.

	Average	2.5% CI	97.5% CI
Total DALY	98.03	91.73	10.37
Total DALY/melanoma	3.67	3.46	3.87
Total DALY/100,000	90.77	84.93	96.02
Total DALY/death[a]	32.70	31.80	33.74
YLL from stage I at diagnosis	2187	1941	2447
YLL from stage II at diagnosis	2572	2241	2925
YLL from stage III at diagnosis	2060	1759	2379
YLL from stage IV at diagnosis	1053	896	1222
YLD from stage 0	183	145	226
YLD from time spent in stage I	365	306	427
YLD from time spent in stage II	120	97	145
YLD from time spent in stage III	1018	821	1243
YLD from time spent in stage IY	245	190	309
Total DALY per 100,000, 1st SA	88.95	83.38	94.33
Total DALY per 100,000, 2nd SA	44.94	42.10	47.77
Total DALY per 100,000, 3rd SA	43.28	40.62	45.94

DALY: disability-adjusted life year; YLD: years lived with disability; YLL: years of life lost; CI: credible interval; SA: scenario analysis.
1st SA: *in situ* melanoma excluded.
2nd SA: pre-2010 Global Burden of Disease approach.
3nd SA: *in situ* melanoma excluded and pre-2010 Global Burden of Disease approach.
[a] Related melanoma death.

4. Discussion

To the best of our knowledge, this is the first study assessing the burden of melanoma according to the local, loco-regional, or distant metastatic stages. In total, 27.8% of the mortality, expressed by YLLs, was generated by stage I patients, 32.7% by stage II, and 26.2% and 13.3% by stages III and IV. For morbidity, expressed by YLDs, 34.8% was linked to localised melanomas, while patients with node metastasis accounted for 52.6% and those with distant metastasis for 12.6% of the YLDs.

Following the results of two previous studies [23,24], we assumed stage 0–II patients who did not relapse to have an impaired melanoma-associated HRQoL for 2 years only. Despite this, the large proportion of patients with localised melanomas who will never relapse accounted for 34.8% of the YLDs. The total DALY, expressed as DALYs in 100,000 inhabitants, was 87.89 in men and 93.64 in women. Women generated 53% of the total DALY, with 59% of melanomas diagnosed in women. The difference between men and women can be accounted for by the lower mean stage at diagnosis in women. The total DALYs we obtained were consistent with the previous studies applying also an incidence-based methodology but with a more simplistic model. In Spain, the DALYs were assessed at 28 and 22 per 100,000 men and women, respectively [16]. In England and Wales, the total DALYs per 100,000 were evaluated at 55 for men and 49 for women [17]. Soerjamataram reported total DALYs per 100,000 of 51 for men and 43 for women in Western Europe [13]. These three studies did not take into account *in situ* melanomas, applied a 3% discount rate and an age weighting function and were based on more pessimistic standard life tables (i.e. life expectancies at birth of 80 and 82.5 years for men and women, respectively, versus 86 in the new tables). Their results should thus be compared with the results of our third

SA, 41.02 and 45.56 per 100,000 men and women, respectively. Holterhues published the Netherlands' burden of melanoma in 2013. Time discounting and age weighting were not applied and their results were close to ours, with 77 DALYs in 100,000 men and 92 in 100,000 women. Murray evaluated the world melanoma DALYs to be 17 in 100,000 [12].

None of the aforementioned studies evaluated the respective weights of local, node-metastatic, and distant-metastatic melanoma. In the studies calculating the proportion of YLL [15–17], it was much higher than YLD, as in our study, where YLL represented 80.4% of the total DALY. This is important in the light of the current debate on the effectiveness of melanoma screening. Some authors argue that numerous melanomas detected by systematic screenings are false positives [3,4] or incipient lesions with extremely small metastatic potential, leading to an artificially increased melanoma incidence that does not save lives but instead increases morbidity through unnecessary aggressive treatments [6]. When considering the hypothesis that dermatologists could guess which melanomas will never metastasize and, therefore, not remove them, this would reduce the YLD of melanoma by 34.8% (670 YLDs), yet the total DALY with only 6.7%. In addition, it is well-known that some rare thin melanomas are, in fact, aggressive. The large number of stage IA patients generates 1003 YLLs, 12.7% of the total YLL. One of the advantages of the DALY methodology is the possibility of comparing burden due to mortality on the one hand and morbidity on the other. In this perspective, we can theoretically compare the 670 YLDs potentially spared when not removing non-aggressive melanomas with the 1003 YLLs due to stage IA melanomas. It is currently very difficult to predict which early melanomas will be fatal on clinical examination. Although demonstrated, the prognostic factors such as Breslow thickness, ulceration and mitotic rates are mostly detected by pathology, typically after excising the melanoma. In conclusion, the comparison of 670 YLDs generated by localised melanoma versus 1003 YLLs resulting from stage IA melanomas supports the hypothesis that efforts for an earlier diagnosis of melanoma make sense. In addition, given the results of our sensitivity analyses (first scenario), we can see that if we eliminate all the *in situ* melanomas, the total DALY (made only of YLD for these patients) would be only slightly reduced. The low YLD provided by *in situ* and IA melanomas is crucial to the debate about the burden related to the excision of incipient melanomas.

This conclusion and, more generally, our results in terms of proportions of DALY/YLL/YLD per stage could be extrapolated to other high-income countries. According to GLOBOCAN 2012 [19], while the melanoma age-standardised incidence rate is much higher in Australia than in Belgium (34.9 versus 12.1 per 100,000), the age-standardised mortality rate is higher in similar proportions (4 versus 1.4 per 100,000). The same calculations for North America and North-Western Europe produced similar results. When assuming that melanomas exhibit the same biology and are treated similarly in these high-income countries, it does not appear unreasonable to assume that the proportions of DALY/YLL/YLD per stage are similar in those countries, the total DALY/YLL/YLD values depending on the incidence in each country. Nevertheless, we underline that in Belgium, interferon is rarely used in stage II–III patients. As this treatment is still commonly used in some countries, and as HRQoL can be altered in these patients, our stage II–III YLD results would be different in these countries.

Our study exhibited some limitations. Firstly, the melanoma model was based on some medical assumptions that may not fully correspond to reality. Although not demonstrated, we, however, believe that the influence of these simplifications on the final results is minimal. An exception may be the assumption that transition probabilities were the same for both genders, which has since been shown to be erroneous [31,32]. If it had been possible to obtain different transition probabilities for males and females, it would have primarily changed the final results by gender, with a much smaller impact on the total results. Secondly, the transition probabilities were based on cohorts of patients diagnosed between 1997 and 2007 with regard to Leiter's database and between 2000 and 2003 for EORTC data. The guidelines for melanoma treatment have changed over time. SNB was not yet a standard treatment in 1997. In addition, this study was based on AJCC staging (seventh edition, 2009) [21], which was probably not taken into account by all Belgian laboratories in 2009 and was obviously not considered in either Leiter's or EORTC database. Thirdly, patients with missing or incomplete stage were re-allocated according to the proportions of patients in the possible stages. Fourth, data for patients included in trial EORTC 18991 may suffer from a selection bias due to the inclusion criteria of this trial. Lastly, the recently made available ipilimumab survival curves [27] did not take into account neither the patients who could not be treated by ipilimumab, due to cerebral metastases, poor general state, or very advanced disease, nor the patients who are currently treated with new promising molecules or drug combinations. We must stress that our results are indicative of the situation at the time of the study. Current research about new molecules for metastatic stage, sometimes also studied as adjuvant treatment in stage III, research about new predictive markers and other possible evolutions in the following years make our results sensitive to time especially for advanced stages. Given the aforementioned limitations, the results should be interpreted with caution.

Finally, the melanoma disease model suggested in this study could be useful for other studies, especially

cost-effectiveness analyses of melanoma screening or treatment.

Contribution

Study concepts: Tromme and Legrand. Study design: Tromme, Legrand, Thomas, and Beutels. Data acquisition: Tromme, Leiter, Suciu, Eggermont, Francart, and Calay. Quality control of data and algorithms: Tromme, Legrand, and Calay. Data analysis and interpretation: Tromme, Legrand, Devleesschauwer, and Speybroeck. Statistical analysis: Legrand, Devleesschauwer, and Speybroeck. Drafting of the manuscript: Tromme, Legrand, and Speybroeck. Manuscript preparation: Tromme and Legrand. Manuscript editing: Tromme, Legrand, and Speybroeck. Manuscript review: Devleesschauwer, Haagsma, Baurain, Thomas, and Beutels.

The corresponding author confirms that she had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

There is no conflict of interest.

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