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Original Research

Cost-effectiveness analysis in melanoma detection: A transition model applied to dermoscopy

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Abstract ***Aim:*** The main aim of this study is to demonstrate how our melanoma disease model (MDM) can be used for cost-effectiveness analyses (CEAs) in the melanoma detection field. In particular, we used the data of two cohorts of Belgian melanoma patients to investigate the cost-effectiveness of dermoscopy.
Methods: A MDM, previously constructed to calculate the melanoma burden, was slightly modified to be suitable for CEAs. Two cohorts of patients entered into the model to calculate morbidity, mortality and costs. These cohorts were constituted by melanoma patients diagnosed by dermatologists adequately, or not adequately, trained in dermoscopy. Effectiveness and costs were calculated for each cohort and compared. Effectiveness was expressed in

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quality-adjusted life years (QALYs), a composite measure depending on melanoma-related morbidity and mortality. Costs included costs of treatment and follow-up as well as costs of detection in non-melanoma patients and costs of excision and pathology of benign lesions excised to rule out melanoma.

Results: The result of our analysis concluded that melanoma diagnosis by dermatologists adequately trained in dermoscopy resulted in both a gain of QALYs (less morbidity and/or mortality) and a reduction in costs.

Conclusion: This study demonstrates how our MDM can be used in CEAs in the melanoma detection field. The model and the methodology suggested in this paper were applied to two cohorts of Belgian melanoma patients. Their analysis concluded that adequate dermoscopy training is cost-effective. The results should be confirmed by a large-scale randomised study.

1. Introduction

The current emergence of numerous new treatments and diagnostic techniques necessitates policy makers to simultaneously consider effectiveness and costs. While health workers naturally go for maximum efficiency, funds are limited and health care payers are faced with hard choices. Cost-effectiveness analyses (CEAs) may help in these choices.

In health economics, effectiveness is often measured by a reduction in mortality and/or morbidity. Combining both is typically expressed as quality-adjusted life years (QALYs) [1]. To compare two scenarios, a CEA contrasts the difference between the two in terms of QALYs to their differences in terms of costs. In order to calculate morbidity, mortality and costs, it is often not feasible to follow cohorts for the complete trajectories of each patient from diagnosis to death. Models are therefore used to simulate the future of patient cohorts. We recently built such a model, further referred to as the 'melanoma disease model' (MDM), to assess the evolution of melanoma patient cohorts and calculate the melanoma burden in terms of localised, node and distant metastatic stages [2].

For melanoma detection, dermoscopy is probably the most studied technique and appears to be widely used among dermatologists in Western countries [3–5]. A meta-analysis of nine studies comparing naked-eye examination with and without dermoscopy concluded that dermoscopy was more accurate than naked-eye examination when practitioners had undergone at least minimal training in dermoscopy. The difference was significant in terms of sensitivity, yet not in terms of specificity [6]. Nevertheless, dermoscopy showed a better specificity when used by well-trained and experienced dermoscopists [7]. In addition, the specificity of dermoscopy was indirectly measured through observation of improvements in the malignant/benign ratio of excised lesions [8]. A study conducted in 13 countries between 1998 and 2007 demonstrated that clinics with dermoscopy perform fewer total number of excisions as compared to clinics without dermoscopy [9].

As dermoscopy improves sensitivity in melanoma detection, dermoscopy may reduce mortality. Additionally, if dermoscopy decreases specificity, it should reduce morbidity by avoiding unnecessary excisions. Nevertheless, to our knowledge, no study has yet demonstrated that dermoscopy reduces morbidity and/or mortality.

This paper proposes a CEA of dermoscopy with or without adequate training based on a slightly modified version of our MDM applied to two Belgian cohorts constituted by melanoma patients diagnosed by dermatologists adequately, or not adequately, trained in dermoscopy. QALYs and costs of both cohorts are compared to assess the cost-effectiveness of adequate dermoscopy training.

2. Material and methods

2.1. The MDM

Fig. 1 shows the MDM previously described in details [2]. In brief, melanoma patients were set to start at one of the diagnostic stages and entered into the model for a certain number of 1-year cycles, until death. The probabilities of moving from one stage to another are called 'transition probabilities' (TPs). All TPs were calculated on a yearly basis, meaning that they were dependent on the time spent by the patient in the previous stage. Our model therefore differs from the classical 'Markov models' often used for CEA, for which TPs are assumed to be time independent [10]. The TPs were based on the data presented in Leiter *et al.* [11], Eggermont *et al.* [12] and Maio *et al.* [13]. For this CEA, contrary to the MDM presented previously [2], we consider that patients can die from any cause at any age (versus only at the end of life expectancy in the previous analysis). These TPs to death from other causes were derived from Belgian mortality tables and are gender- and age dependent [14].

Melanoma patients from the DEPIMELA (from "Dépistage" – detection, in French – and "Melanoma") study [15] were included in the present study. Briefly, the DEPIMELA study was conducted in

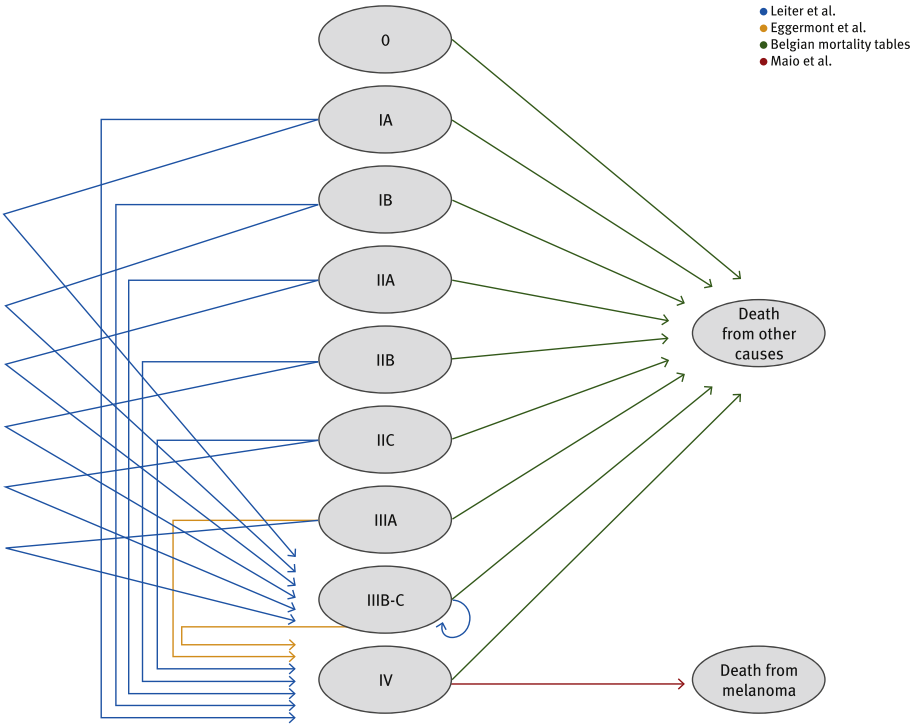

Fig. 1. Melanoma disease model. The duration of one cycle was set to 1 year. During each cycle, every patient can stay in the same state or move to another state following one of the model's transitions. Transition probabilities (TPs) associated to blue and orange arrows were estimated using the data from, respectively, Leiter et al. [10] and Eggermont et al. [11]. TPs to death from any cause (green arrows) were obtained from the Belgian mortality tables [13]. TPs from stage IV to death due to melanoma were based on the results of Maio et al. [12].

2009–2010, involving 36 volunteer dermatologists recruited from private and public hospital practices. The patients were categorised, according to the level of dermoscopy training undergone by the dermatologist who took the decision to excise, with little training (less than 10 h) classified as group A, and adequate training (over 10 h complemented by self-training) as group B. Stages of melanoma patients were recorded according to the 'tumour–node–metastasis' (TNM) staging [16]. These were translated into American Joint Committee on Cancer (AJCC) 2009 stages [17]. All patients classified as T1b or higher underwent sentinel node biopsy (SNB), but their results were not collected. We therefore derived the probabilities of having a positive SNB from the results published by Ross *et al.* [18]. A sensitivity analysis (SA) excluded the nodular sub-type melanomas.

2.2. Costs

Costs were assumed to be only direct medical costs arising to the health care payer (i.e. the health care system costs and the patients' personal copayments combined), according to Belgian guidelines for CEA [19]. Treatment costs and follow-up costs were assessed through the 2012–2013 patients who participated in the health-related quality of life (HRQoL) study described previously [20]. Briefly, the patients were categorised in eight groups according to the 2009 AJCC classification (0–IA, IB–II, III and IV), each stage being sub-divided into treatment and remission phases. In addition to HRQoL questionnaires, patients were asked to complete a questionnaire about their personal melanoma-related costs. The questions covered the external medical consultations and external pharmacist costs. Current Belgian unit costs are presented in Table 1. We also included the hospital bill costs for those patients who received the full treatment or follow-up in the St Luc hospital. In each of these eight groups, the costs were estimated based on all patients (if less than 20) or on a random sample of 20 patients. Given that the HRQoL study included stage 0–I–II patients for only 2 years, the costs for the third year were assumed to remain identical as those of the second year, and from the fourth year onwards, the mean costs were assessed by means of expert's opinion. According to Belgian guidelines, future costs were discounted at a 3% rate [19]. Total treatment and follow-up costs were calculated based on the future history of patients of groups A and B as predicted by our MDM.

Detection costs were derived from the DEPIMELA study [15]. These included screening costs and benign lesion excision costs. The screening costs included the consultation cost, added to dermoscopy cost when applicable, for all patients exhibiting neither melanoma nor suspicious lesions. The costs of excising benign suspicious lesions included the surgery and pathology costs.

Table 1
Unit costs in Belgium (2013), expressed in €.

	Cost (in €)
Personal costs	
General practitioner's consultation	23.67
Nursing at home	13.78
Psychologist's consultation	50,00
Physiotherapist's consultation	21.96
Alternative medicine consultation	50.00
Healing cream	40.12
Bandages	20.00
Antibiotic treatment	10.54
Analgesic treatment	12.23
Anxiolytic treatment	57.76
Support stockings	100.00
Detection costs	
Dermatologist's consultation	28.88
Dermoscopy	6.39
Cutaneous tumour excision with suture	54.1
Cutaneous tumour pathology	62.02
Immunochemistry[a]	25.41

[a] We assumed that two immunostains were performed in a number of benign nevi equivalent to the number of melanomas in each group [30].

2.3. QALY calculations

Patients from groups A and B were entered into the MDM. To calculate QALYs, each year of life from diagnosis to death had to be weighted by a number between one (perfect HRQoL) and zero (death), so-called 'utility'. We used recently published utilities based on EQ-5D-5L (EuroQol – 5 Dimensions – 5 Levels) instrument [20]. As stage 0–I–II patients were assumed to exhibit the same HRQoL as the general population from the third year after diagnosis onwards, we applied single year of age EQ-5D-3L Belgian population norms for these patients [21] to assess their QALYs from the third year after diagnosis to death. According to Belgian guidelines, the QALYs were discounted at a rate of 1.5% [19].

2.4. Probabilistic sensitivity analysis

To jointly investigate the impact of uncertainty in the model parameters, a probabilistic sensitivity analysis (PSA) was performed [22]. The QALY and cost computations were repeated 1000 times considering for each analysis, random draws for the values of parameters, from a probability distribution reflecting parameter uncertainty. Uncertainty was considered for TPs, utilities, hospital costs, personal costs and detection costs. Probability distributions used were gamma for the TPs (with parameter values determined based on the confidence interval of the estimated hazard), beta for utilities (with parameter values based on the observed mean and standard error of the mean), and gamma for the hospital costs (idem). Uncertainty for detection costs was calculated from the number of screening consultations needed to find a melanoma and the number of benign suspicious lesions to excise needed to diagnose a melanoma for each dermatologist in groups A and B, respectively. To capture the uncertainty in these parameters, they were modelled as Poisson distributions with means corresponding to the observed values. Uncertainties in the personal costs were modelled in a similar way, considering binomial distributions for the proportions of patients who had access to external consultations with fixed current Belgian unit costs for those. For each of the 1000 PSA replications, the QALY and cost differences between both groups were calculated and plotted on a so-called 'cost-effectiveness plane' [1].

3. Results

3.1. Results derived from the DEPIMELA study

During 1 year, 94 melanomas were diagnosed in group A and 74 in group B. The numbers of melanomas were higher than those reported in the DEPIMELA study due to the false-negative melanomas having been excluded in the previous study due to a different endpoint [15]. All 168 melanoma patients were node negative on clinical examination. Table 2 presents the patient characteristics and distribution according to the translation from TNM classification to AJCC 2009 staging, SLN result being derived from Ross *et al.* [18]. The second part of the table presents the same data according to SA excluding the nodular sub-type melanomas. Table 3 displays the number of screened patients and the number of benign lesions excised in order to find a melanoma according to the DEPIMELA results and the costs associated with these screenings and excisions.

3.2. Costs assessments

Hospital costs were obtained from a random sample of 20 patients in each group, except for stage III patients in treatment (14 patients) and stage IV patients in remission (11 patients). This resulted in 145 hospital bills to estimate hospital costs. The patients' personal medical costs were based on 253 questionnaire responses. Mean costs per stage are presented in Table 4.

3.3. CEA planes

Our PSA led to an average decrease in cost of 4420€ (95% credibility interval [CI]: 5821, 2972) and an average increase in QALY of 2.03 (95% CI: 1.99, 2.07) in favour of group A. The CEA plane (Fig. 2) confirms that group B dominates group A, meaning that 'dermoscopy performed by adequately trained dermatologists' is found to be more effective and less costly than 'dermoscopy performed by non-adequately trained dermatologists'. This result is robust, as all the PSA dots are in the south-east quadrant meaning that for all 1000

Table 2
Melanoma patients from the DEPIMELA study.

	Mean age	Gender ratio M:F	*In situ*	IA	IB	IIA	IIB	IIC	IIIA	IIIB	Total
Group A	51.8	0.45	19	53.82	8.85	3.08	2.58	0.45	4.07	2.16	94
Group B	45.6	0.90	28	39.40	3.53	0	0.63	0	1.82	0.62	74
Group A, SA	51.6	0.44	19	52.86	8.85	2.31	1.95	0.45	3.80	1.79	91
Group B, SA	45.6	0.90	28	39.40	3.53	0	0.63	0	1.81	0.62	74

Abbreviations: M: male; F: female; SA: sensitivity analysis excluding nodular melanomas.
Numbers are not whole numbers because tumour–node–metastasis were translated into probability of American Joint Committee on Cancer classification according to Ross [18].

Table 3
Number of patients to screen and number of benign lesions to excise per melanoma diagnosed; detection costs per melanoma diagnosed, expressed in €

	Number of patients to screen	Costs of screening (in €)	Number of benign lesions to excise	Costs of benign lesions excised (in €)	Total detection costs (in €)
Group A	89.94	2597	9.71	1153	3751
Group B	91.30	3220	7.70	920	4140

Table 4
Costs according to American Joint Committee on Cancer stages, excluding screening costs, expressed in € and utilities

	Periods	Hospital costs	Personal costs	Utilities
0/IA-T	3 First months	1132 (874–1423)	95 (76–115)	0.687 (0.641–0.731)
0/IA-R	4th to 36th month, per year	280 (171–414)	82 (57–112)	0.809 (0.773–0.843)
0/IA-R	37th month to death, per year	44*	0*	0.809 (0.773–0.843)
IB/II-T	3 First months	3589 (3190–4011)	199 (140–262)	0.579 (0.486–0.670)
IB/II-R	4th to 24th month, per year	1061 (792–1369)	227 (166–293)	0.802 (0.763–0.838)
IB/II-R	37th month to death, per year	44*	0*	0.802 (0.763–0.838)
III-T	3 First months	6840 (5506–8317)	768 (505–1046)	0.535 (0.393–0.674)
III-R	From 4th month, per year	1680 (1134–2331)	576 (388–799)	0.703 (0.659–0.745)
IV-T	From start of treatment, per year	82,853 (66,301–101,221)	406 (210–628)	0.583 (0.524–0.641)
IV-R	From start of remission, per year	2349 (1804–2964)	81 (6–171)	0.796 (0.701–0.877)

*No uncertainty considered (mean costs assessed by means of expert's opinion).
Observed mean value and 95% credibility intervals (CIs) representing uncertainty in our estimation were reported. These 95% CIs are based on actual quantiles for hospital costs and utilities and on simulation for personal costs.

PSA simulations, QALYs in group B were higher than QALYs in group A and costs in group B were lower than costs in group A. The SA that removed nodular melanoma from the cohort led to the same conclusions (Fig. 3). The vertical direction of the ellipse-shaped cloud in the CE planes indicate that there is more parametric uncertainty in relation to the costs than QALY differences between both groups, given the scale of the axes.

4. Discussion

To the best of our knowledge, this is the first study that sought to assess the cost-effectiveness of dermoscopy. This technique has proven to enhance sensitivity when performed after minimal training, as well as specificity when performed by well-trained and experienced dermoscopists. Yet these observations have never been investigated in a CEA, in which the outcomes were expressed in QALYs. The study at hand provides an MDM which could be used to derive QALYs and costs for any patient cohort, requiring only information on the stage at diagnosis along with local costs for treatment and follow-up of each melanoma stage, as well as updated information on TPs if new treatments are considered.

We use this model to perform a CEA of adequate training in dermoscopy, entering into the MDM two cohorts of patients as well as treatment and follow-up cost data. In addition to these costs, detection costs were included as part of the melanoma-related costs.

The CEA plane indicated that dermoscopy performed by adequately trained dermatologists dominated significantly dermoscopy performed by non-adequately trained dermatologists, meaning that the first situation was consistently more effective and less costly than the second. The so-called 'fast-growing melanomas' (FGMs) represent, according to some authors, a large proportion of 'killer' melanomas. FGMs frequently elude early detection due to the difficulty for the patient and physician, including dermoscopists, to diagnose them. In addition, these are almost never detected in

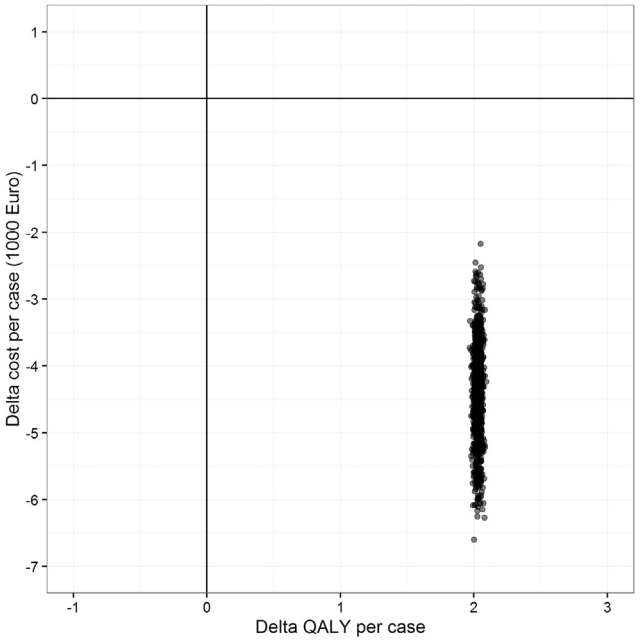

Fig. 2. Cost-effectiveness plane. Delta QALY = QALY B − QALY A. Delta costs = costs B − costs A. Each dot represents for one replication of the probabilistic sensitivity analysis the results obtained for the difference in QALY per subject (delta QALY per case) and for the difference in cost per subject (delta cost per case) for group B minus group A. A positive value for delta QALY represents an advantage of group B over group A in terms of effectiveness, while a negative value for delta cost represents a higher cost for group A compared to group B. Abbreviation: QALY, quality-adjusted life year.

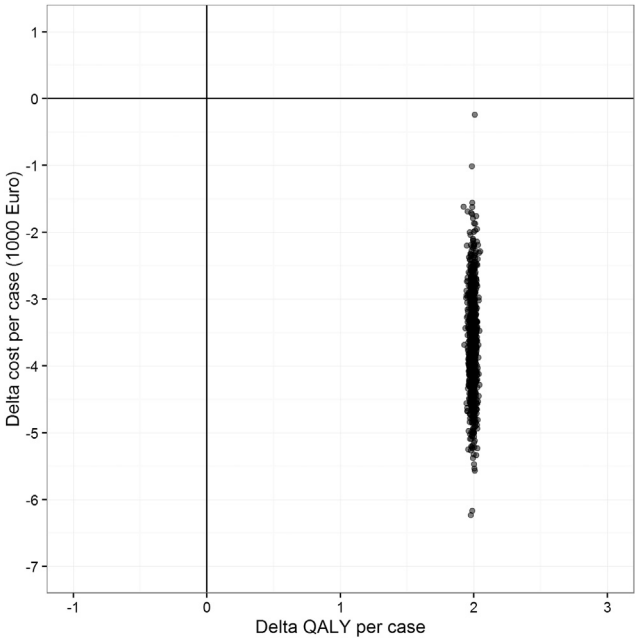

Fig. 3. Cost-effectiveness plane, sensitivity analysis excluding nodular melanomas. Delta QALY = QALY B − QALY A. Delta costs = costs B − costs A. Each dot represents for one replication of the probabilistic sensitivity analysis the results obtained for the difference in QALY per subject (delta QALY per case) and for the difference in cost per subject (delta cost per case) for group B minus group A. A positive value for delta QALY represents an advantage of group B over group A in terms of effectiveness, while a negative value for delta cost represents a higher cost for group A compared to group B. Abbreviations: QALY, quality-adjusted life year.

routine screenings due to their significant biological aggressiveness and the fact that they do not preferentially affect patients at high risk for melanoma [23–25]. As FGMs almost always originate from the nodular pathological sub-type, we conducted a SA excluding nodular melanomas. We could, in fact, consider their diagnosis to be purely a matter of chance, and their aggressiveness may lead to an artificial and on balance equal loss of QALYs in groups A and B. The results of this SA, however, do not change our conclusions.

Our study has some limitations. First, patients were not randomised and we cannot exclude that the behaviour of the patients was influenced by the dermatologist they chose to consult. As a main example, it is possible that patients who consulted dermatologists adequately trained in dermoscopy were more careful with their moles and consulted faster when a lesion had appeared or changed. Dermoscopists are also often more motivated to perform total body examinations [26]. Second, the cohorts included in the MDM are rather small and the costs are estimated on a sub-optimal number of patients. Third, our QALY assessment did not include the decreased HRQoL generated by the surgery of benign lesions excised to rule out melanomas. Fourth, our cost assessment did not take into account costs related to the dermatologist's training, nor the patients' travel costs and the indirect costs related to the loss of productivity owing to inability to work or death resulting from melanoma or from undergoing diagnostic procedures and receiving treatment.

However, despite these limitations, the MDM we suggest has the advantage of being closer to reality compared to most models used until now. Indeed, it is as much as possible informed by empirical studies and includes time-dependent TPs. Besides dermoscopy, the MoleMate system is another non-invasive system aimed at improving melanoma detection in primary care. Due to its more complex nature, this system is more expensive. A randomised controlled trial has already demonstrated its efficacy among general practitioners versus best practice [27]. Nevertheless, when this efficacy has to be translated in effectiveness and valued in terms of QALYs for a CEA, one of the main obstacles is the lack of data with which to assess the evolution of diagnosed melanomas [28]. The authors of this CEA used a simple assessment suggested by Losina in a previously published CEA of melanoma screening [29]. Based on experts' opinion, they predicted a 10% progression rate of melanoma from one stage to another annually. Our

MDM could be expected to provide more reliable results in such CEAs related to melanoma detection.

As a result, this paper provides an opportunity to discuss the cost-effectiveness of training in dermoscopy, which should be ideally confirmed with a large multicenter and randomised study. However, dermoscopy has become a standard of care in all high-income countries that would have adequate funds to set up such a study. It will remain ethically challenging to randomise patients into groups examined by adequately trained dermatologists and 'insufficiently trained' dermatologists. Hence, model-based evaluations such as ours will need to continue providing insights in cost-effectiveness research. The main interest of this paper therefore resides in its proposal of a new model for conducting CEA in the melanoma detection field and, in a wider sense, for all melanoma screening tests or preventive campaigns.

Conflict of interest statement

None declared.

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