Cost-Effectiveness of the addition of Reflectance Confocal Microscopy in the diagnostic pathway of skin cancer

W. F. ten Bolscher

Master thesis Health Sciences

University of Twente

6-9-2017

Preface

Before you lies the Master thesis “Cost-Effectiveness of the addition of Reflectance Confocal Microscopy (RCM) in the diagnostic pathway of skin cancer”. From February 2017 till September 2017 I was conducting this study into the costs and effects of this new technology and trying to model their interactions in a clinical setting. The aim was to fulfill the graduation requirements of the Master study Health Sciences at the University of Twente (UT).

In my previous studies, Health Sciences and Technical Medicine, I gained a lot of knowledge about the healthcare sector and its institutions. So when the opportunity presented itself to combine these studies and gain hands-on experience inside the Netherlands Cancer Institute, I knew I had to take it. Together with my supervisors, W. H. van Harten and V. Retèl, and two physicians, Y. Elshot and M. B. Crijns, we defined the research question.

After the initial literature study and getting to know the problem, the new technique and its current literature, I decided I also wanted to know the other side of the story. The patients are in the center of the problem, so gaining some clinical experience and seeing the patients was of great importance. Together with Yannick, I looked at a lot of RCM images and got to see patients being examined, diagnosed and treated. This really showed me the potential benefit of the new technique and got me more involved in the research.

The data collection was a huge obstacle, because the retrospective dataset was initially not suited for the analyses we wanted to perform and the financial and activity data was difficult to get and interpret. It took a lot of effort, discussions, appointments with specialists and hours of digging in the datasets to get a viable and valid dataset that could be used to build the model. The numerous departments involved, ambiguity of the problem and data required a lot of planning and organizational skills to overcome. To validate the data, the financial records of the NKI were used and a questionnaire about the intended use and referral patterns of RCM was drafted and sent to the dermatologists.

All these steps led to the modelling and validation phase, which went smooth and allowed me to finish this master thesis on schedule. Next target will be to, in close collaboration with Yannick Elshot, convert this thesis into a published paper.

I would like to end this preface by thanking all the people who were involved in creating this thesis, in particular Valesca Retèl, Yannick Elshot, Wim van Harten and Marianne Crijns for their excellent guidance, support and supervision during the whole project. I would also like to thank the other dermatologists of the NKI, my colleagues at the PSOE (NKI) and HTSR (UT) for their cooperation and afford to make this a wonderful experience.

I hope you will enjoy reading my thesis.

Wouter ten Bolscher

6-9-2017

Introduction

Skin cancer is likely to be the most common cancer worldwide[1]. Skin cancer can be divided into two subgroups: melanoma and non-melanoma. The non-melanomas mainly consist of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In the Netherlands melanoma, BCC and SCC have an incidence of around 5.500, 37.500 and 10.000 patients respectively.[2,3] In Europe the incidence of malignant melanoma, which is only a small but important part of the all skin cancers, is the ninth highest of all cancers with more than 100.000 new cases in 2012.[4] The survival rate differs between the types. The non-melanoma cancers have a 5-year survival rate of 95% and higher. The survival rate of melanoma depends on the stage of the cancer at diagnosis. When the cancer is discovered in an early stage the survival rate is similar to the non-melanoma. When it is discovered at a later stage the survival rate drops drastically to 20-40%.[2,3] Currently, diagnosis is performed by dermatoscopy, biopsy or diagnostic excision. Because of the low sensitivity of dermatoscopy many unnecessary biopsies and excisions are performed. Excisions and biopsies can be painful, can causes scarring and there is waiting period of around two weeks for the test results which causes significant anxiety.[5] Reflectance confocal microscope (RCM) has been developed to make faster diagnosis possible and reduce the number of unnecessary excisions. RCM is a non-invasive method enabling checking of suspicious lesions at cell level. A study performed by Pellacani et al. estimated that RCM would result in a reduction of 4320 unnecessary excisions per million inhabitants and a net costs saving of 260.000 euro per year per million inhabitants.[6] Clinical effectiveness studies have shown that RCM is significantly more sensitive and specific in diagnosing skin lesions compared to dermatoscopy. However due to higher costs, high prevalence of skin cancer and RCM being more time consuming it is not a viable alternative and is only considered as an addition to dermatoscopy in equivocal cases.[5,7–9] The objective of this study is to assess the cost-effectiveness of RCM as an addition to dermatoscopy on equivocal lesions compared to usual care (only dermatoscopy) in the diagnostic pathway of skin cancer based on retrospective clinical cohort data and literature study data.

Methods and Materials

The diagnosis of skin cancer is currently based on the clinical-dermatoscopic pathway. Dermoscopy, or skin surface microscopy, is a noninvasive device that allows the in vivo evaluation of cutaneous tumors at 10x magnification. By using fluid immersion or polarized light, the reflectivity of the skin is reduced, enhancing the transparency of the stratum corneum. This results in the visualization of specific structures and distribution of melanin related to the epidermis, dermoepidermal junction, and papillary dermis, not visible to the naked eye.[10]

Reflectance confocal microscopy is based on the differences in light reflection between different tissues. A near infrared laser sends a beam of coherent laser light through lenses to accurately distribute the light to a specified focal point. At the focal point, the light is reflected and passes through lenses, so eventually all unfocused light is filtered out by a pinhole, resulting in better quality images. The intensity of the reflected light depends on the cellular contents which is measured by the detector and displayed in a greyscale image. The wave length and power of light are important factors to consider when using confocal microscopy on human tissue. They define how deep the light bundle can penetrate the skin, but can also cause damage to the skin if too high. Most commonly a near infrared beam with a wavelength of 830nm is used in combination with a power which is lower than 30mW. This configuration can reach a penetration depth of 200-300µm and causes no damage to the skin.[5,11,12] For this research the VivaScope 1500/3000® systems have been used (CaliberID, Henrietta, NY, U.S.A.; MAVIG GmbH, München, Germany).

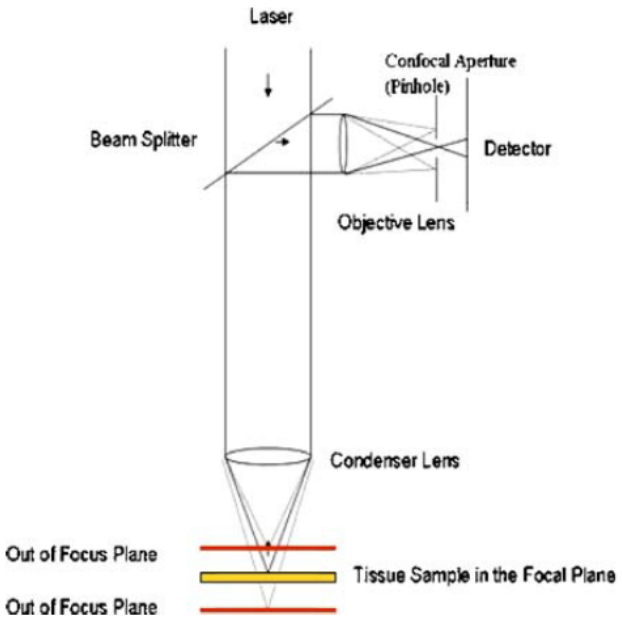

Figure 1 Discription and explanation of used technologies

Modeling and Analysis

Effectiveness analysis of retrospective cohort

The retrospective cohort was analyzed to assess the clinical effectiveness of the Vivascope system. This analysis was used as the basis of the created models. The output of this analysis is the sensitivity, specificity and number needed to excise (NNE) of RCM in the diagnosis of dermatoscopic equivocal skin lesions. Subtyping of the lesions was not included due to lack of detailed information and literature on this topic. For the created models, especially important for BCC, it was assumed that subtyping of lesions is possible using RCM.

Markov model

A patient level model has been constructed for melanoma, facial pigmented macules (FPM) and BCC diagnosis comparing two different strategies: usual care (dermatoscopy only) and dermatoscopy with

additional RCM. This study adopts a healthcare perspective and simulates a hypothetical cohort of 1000 patients with an average age which is the mean age of the modeled group. For melanoma this was 54,3 years, 66,0 years for FPM and 63,6 years for BCC. The model was based on the patient flow inside the dermatology outpatient clinic of the Netherlands Cancer Institute (NKI)(Amsterdam, The Netherlands), and summarized in a clinical flowchart. The flowchart has been constructed based on the expert opinion of two dermatologists at NKI. In current practice, in the majority of dermatoscopic suspect or equivocal lesions, either a diagnostic excision or biopsy is performed. At low suspicion of malignancy, a short-term follow-up is performed, after which the lesion is either deemed benign or histological assessment is performed. The addition of RCM would potentially result in equivocal lesions being diagnosed as either benign or malignant, with a similar sensitivity and increased specificity (Figure 2).

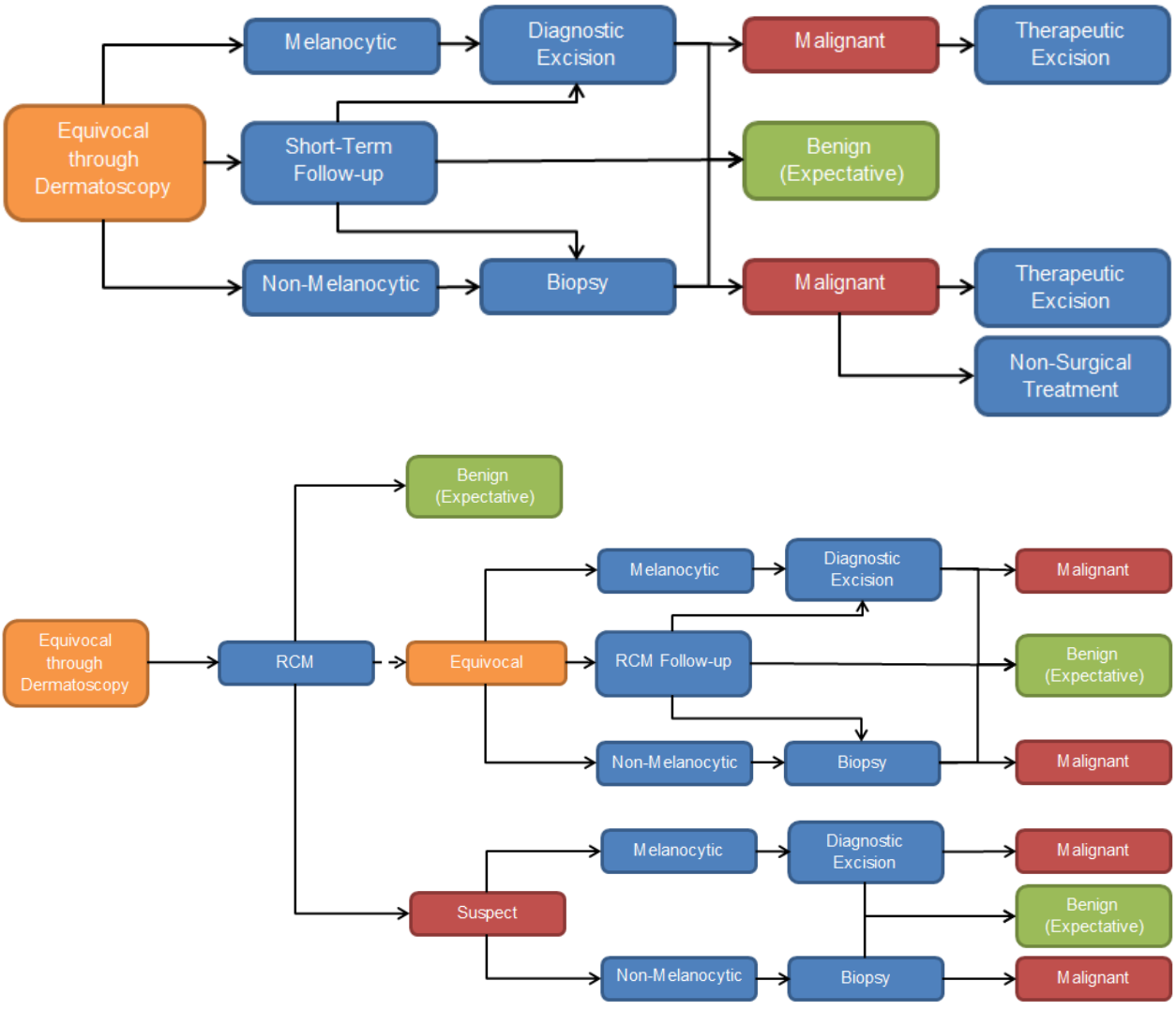

Figure 2 Clinical flowcharts of current diagnostic pathway of dermatoscopic equivocal lesions (above) and the expected flow with the addition of RCM in the diagnostic pathway (below)

The Markov model is constructed using a yearly cycle length and a 15-year time horizon has been adopted. This specific time horizon was chosen because melanoma has an elevated mortality rate lasting till 10 years after treatment. The assumption is made that initially unidentified patients will be identified within 5 years, adding up to a potential of 15 years of elevated mortality due to initial melanoma.

Figure 3 Health states of Markov model for melanoma (below), BCC(left, above) and LM(right, above)[5]

In the melanoma model patients could end up in any of the following seven mutually exclusive health states as defined by Edwards[5] (figure 3). The BCC model relies on two and the FPM model on five mutually exclusive states (figure 3).

Model inputs and patient description

The model inputs were based on a retrospective cohort and literature study. Additionally, the following assumptions have been made: a three-month follow-up gives certainty on the diagnosis, all patients with an equivocal outcome after dermatoscopy have been referred to undergo RCM and the included patients give a good representation of a normal clinical setting.

Patients entered the retrospective cohort if their first RCM consult took place in the period from the first of March 2016 till the 14th of June 2017 following an equivocal dermatoscopic outcome. The patient group comprised of 695 patients with an average age of 60,5 years and consists of 287 men and 408 women. These 695 patients represented a total of 940 lesions. Data entries were excluded when patients were tested out of curiosity or on patient request (n=41), when diagnosis could not be confirmed by follow-up or histopathology (n=7), when images were not possible, inadequate or not available (n=25), when there were double entries (n=11) or if patient or lesion data was not available (n=14). Thirty-five patients were excluded because they were not registered patients of NKI (n=4), had histopathological confirmed malignancies (n=19), or were pre-surgically scanned dermatoscopic "classic" melanoma (n=12).

After exclusion of 133 patients, a split was made based on differential diagnose to create the datasets for the three models: melanoma, FPM and BCC, respectively 211, 98 and 265 patients. Twelve patients had a differential diagnose with a double indication and were therefore taken into account for both respective models. Probabilities, patient characteristics, sensitivity and specificity were derived from this data. All further data was based on literature or assumptions.

The costs are based on medical charts and/or the Dutch guideline on costing studies. The financial administration of the NKI has been used as a reference. A prediction is made with regard to the implementation of RCM in clinical practice and costs for RCM examination are based on this prediction. It is assumed that 700 patients per year will be scanned. The scanning will be performed by a Specialist Nurse with a VivaScope 1500 (CaliberID, Henrietta, NY, U.S.A.; MAVIG GmbH, München, Germany) after which a dermatologist will review the images. Purchasing costs of the VivaScope (CaliberID, Henrietta, NY, U.S.A.; MAVIG GmbH, München, Germany) hardware, costs of consumables, maintenance, overhead, training and staff costs are taken into account for the costs of RCM while the useful lifespan of the device is assumed to be 10 years. Utility data is based on the systematic review included in the research of the NHS by Edwards et al and based on EQ5D methodology. All of the important input parameters are shown in table 1.

	Value	Distribution	Reference
Parameter specific to Melanoma model			
Mean age	54,26	NA	Retrospective cohort
Standard deviation of age	14,87	NA	Retrospective cohort
Sensitivity RCM	0,93	Beta (α=92,65; β=7,35)	Retrospective cohort
Specificity RCM	0,7	Beta (α=70,06; β=29,94)	Retrospective cohort
Probability the dermatoscopic equivocal lesion treated as suspected melanoma	1	NA	Assumption
Ratio of malignancies in equivocal lesions	0,28	Beta (α=27,76; β=72,24)	Retrospective cohort
Probability the localization is head and neck	0,15	Beta (α=14,69; β=85,31)	Retrospective cohort
Probability patient is male	0,45	Beta (α=45,02; β=54,98)	Retrospective cohort
Probability patients is female	0,55	Beta (α=54,98; β=45,02)	Retrospective cohort
Percentage of patients needing extra surgery	7,50%	Beta (α=7,50; β=92,50)	Assumption
Patients per lesion	0,86	Beta (α=86,12; β=13,88)	Retrospective cohort
Probability cancer stage is In Situ	0,6		Assumption (based on Edwards[5])
Probability cancer stage is Stage 1	0,4		Assumption (based on Edwards[5])
Probability of identification	0,35	Beta (α=35; β=65)	Assumption (based on Edwards[5])
Probability of cancer progression	0,153	Beta (α=15,30; β=84,70)	Assumption (based on Edwards[5])
Yearly mortality rate of melanoma patients in first 5 years after identification			
Stage 1	0,0112		Derived from Balch et al[13]
Stage 2	0,0463		
Yearly mortality rate of melanoma patients in second 5 years after			

identification			
Stage 1	0,000237		Derived from Balch et al[13]
Stage 2	0,00345		
Parameter specific to BCC model			
Mean age	63,57	NA	Retrospective cohort
Standard deviation of age	13,02	NA	Retrospective cohort
Sensitivity RCM	0,97	Beta (α=96,67; β=3,33)	Retrospective cohort
Specificity RCM	0,84	Beta (α=83,56; β=16,44)	Retrospective cohort
Probability the dermatoscopic equivocal lesion treated as suspected BCC	1	NA	Assumption
Ratio of malignancies in equivocal lesions	0,65	Beta (α=64,66; β=35,34)	Retrospective cohort
Probability the localization is head and neck	0,51	Beta (α=50,96; β=49,04)	Retrospective cohort
Probability patient is male	0,42	Beta (α=41,51; β=58,49)	Retrospective cohort
Probability patients is female	0,58	Beta (α=58,49; β=41,51)	Retrospective cohort
Percentage of patients needing second biopsy	2%	Beta (α=2; β=98)	Assumption
Patients per lesion	0,64	Beta (α=63,70; β=36,30)	Retrospective cohort
Parameter specific to FPM model			
Mean age	65,96	NA	Retrospective cohort
Standard deviation of age	11,71	NA	Retrospective cohort
Sensitivity RCM	0,91	Beta (α=90,63; β=9,38)	Retrospective cohort
Specificity RCM	0,76	Beta (α=75,76; β=24,24)	Retrospective cohort
Probability the dermatoscopic equivocal lesion treated as suspected BCC	1	NA	Assumption
Ratio of malignancies in equivocal lesions	0,33	Beta (α=32,65; β=67,35)	Retrospective cohort

Probability the localization is head and neck	0,89	Beta (α=88,78; β=11,22)	Retrospective cohort
Probability patient is male	0,44	Beta (α=44,21; β=55,79)	Retrospective cohort
Probability patients is female	0,56	Beta (α=55,79; β=44,21)	Retrospective cohort
Percentage of patients needing extra surgery	30%	Beta (α=30; β=70)	Assumption
Patients per lesion	0,97	Beta (α=96,94; β=3,06)	Retrospective cohort
Annual probability of recurrence first 5 year	0,02		Assumption(based on Edwards et al. [5])
Annual probability of recurrence second 5 years	Exponentially declining till 0		Assumption(based on Edwards et al. [5])
Generic parameters	Value	Distribution	Reference
Utilities general population			
50-59 y/o	0,798	Beta (α=79,80; β=20,20)	Sullivan et al[14]
60-69 y/o	0,774	Beta (α=77,40; β=22,60)	
70-79 y/o	0,723	Beta (α=72,30; β=27,70)	
>=80 y/o	0,657	Beta (α=65,70; β=34,30)	
Metastatic or terminal melanoma (stage IV)	0,585	Beta (α=58,50; β=41,50)	Tromme et al.[15]
	(-0,00029 per year after 55)	Beta (α=0,03; β=99,97)	
One off disutilities			
Melanoma management (stage I)	-0,01 (-0,00029 per year after 55)	Beta (α=1; β=99)	Tromme et al.[15]
Melanoma management (stage II)	-0,037 (-0,00029 per year after 55)	Beta (α=3,7; β=96,3)	Tromme et al.[15]
Excision and biopsy	-0,002 (-	Uniform (range: 0,001- 0,003)	Seidler et al.[16] & Edwards et al.[5]

	0,004 when in head or neck)		
Anxiety of waiting on results of biopsy	-0,019	Uniform (range: 0,009- 0,039)	Edwards et al[5]
Scarring in head or neck (from initial diagnostic excision and biopsy)	-0,016	Uniform (range: 0,006: 0,026)	Seidler et al.[16]
Scarring in head or neck (wider surgical excision(Therapeutic excision))	-0,017	Uniform (range: 0,007- 0,027)	Seidler et al.[16]
Costs	In euro's		
cost consult	86,-	Gamma (α=43; β=2)	Reference costs for costing studies[17]
costs RCM examination	106,54	Gamma (α=53,27; β=2)	Derived from VivaSscope costs and assumptions
cost biopsy	243,67	Gamma (α=121,84; β=2)	CZ 18[18]
Diagnostic excision	671,99	Gamma (α=121,84; β=2)	CZ 18[18]
Therapeutic excision	671,99	Gamma (α=335,99; β=2)	CZ 18[18]
Discounting			
Effects	1,50%		Assumption
Costs	4%		Assumption

Table 1 Input parameters of the melanoma, BCC and FPM model

Analysis

The output of the models was the Incremental cost-effectiveness ratio (ICER), calculated with the function: $ICER = \frac{Costs\ RCM - Costs\ usual\ care}{Effects\ RCM - Effects\ usual\ care}$.

This has first been calculated by using deterministic values for all the parameters and again with probabilistic values to account for uncertainty. Distributions are based on literature and data if available, otherwise plausible assumptions have been made. The model used Monte Carlo simulation with 10.000 iterations to create a valid result.

Sensitivity analysis

In addition to the deterministic and probabilistic analyses a one-way sensitivity analysis has been conducted. The parameter values of all models have been increased and decreased with 20%, resulting in a tornado diagram showing the impact of these changes on the ICER.

A few specific analyses have been done to evaluate subgroups or plausible scenarios. Firstly, the subgroup of head neck patients. This subgroup has a 15% probability on quality of life reducing scars. Secondly, a scenario is analyzed that RCM has the same sensitivity and specificity as biopsy or diagnostic excision. A recent study suggests that RCM has comparable effectiveness as biopsies, consequently this analysis is a plausible scenario.[19]

Results

Effectiveness

The sensitivity and specificity of the models for RCM are based on the retrospective cohort and are respectively 0,96 and 0,89 for the BCC group, 0,92 and 0,76 for the melanoma group and 0,91 and 0,76 for the FPM group. The number needed to excise (NNE) for RCM is 1 melanoma for every 1,84 excisions performed. BCC has a ratio of 1 every 1,09 excisions and FPM 1 in every 1,55.

	Melanoma	BCC	FPM
Sensitivity	0,92	0,96	0,91
Specificity	0,76	0,89	0,76
NNE	1/1,84	1/1,09	1/1,55

Table 2 Effectiveness of RCM within the selected subgroups (melanoma, BCC and FPM)

Deterministic results

The melanoma model shows only a small QALY gain over the 15-year time period. The overall QALY's, with usual care or the diagnostic pathway with the addition of RCM, per person in a 15-year time period are 9,25 and 9,26 respectively, resulting in an incremental effect of 0,0041 QALY. The costs of the two diagnostic methods are estimated to be around €1021 and €831 respectively resulting in an incremental cost of €-190, favoring RCM. The deterministic analysis of melanoma consequently shows dominance over usual care (table 3).

The BCC model also shows only a small QALY gain over the 15-year time period. The overall QALY, with usual care or the diagnostic pathway with added RCM, per person in a 15-year time period are 8,48 and 8,49 respectively, resulting in an incremental effect of 0,0081 QALY. The average costs of the two diagnostic methods are estimated to be around €1269 and €1109 per patient respectively, resulting in an incremental cost of €-160, favoring RCM. Since there is a gain in QALY at a lower cost, the diagnostic pathway with the addition of RCM is dominant over usual care (table 3).

The last model, for FPM, shows a QALY gain of 0,0117 since the overall QALY, with usual care or the diagnostic pathway with added RCM, per person in a 15-year time period are 8,19 and 8,21 respectively. The average costs of the two diagnostic methods are estimated to be around €579 and €504 per patient respectively, resulting in an incremental cost of €-75, favoring RCM.

In all models the difference in disutilities, between with or without RCM, is around 0,1% of the cumulated utility.

		Costs dermatoscopy	Costs with RCM	QALYs dermatoscopy	QALYs RCM	Incremental Costs	Incremental QALY's	ICER
Melanoma	Deterministic	1021 (995 | 1048)	831 (791 | 871)	9,25 (9,11 | 9,40)	9,26 (9,11 | 9,41)	-190 (-209 | -172)	0,0041 (-0,166 | 0,174)	Dominant
	Probabilistic	1021 (903 | 1140)	830 (688| 973)	9,25 (8,66 | 9,84)	9,26 (8,67 | 9,84)	-191 (-258 | -123)	0,0057 (-0,166 |0,178)	Dominant
BCC	Deterministic	1269 (1231 | 1306)	1109 (1079 | 1138)	8,48 (8,31 | 8,65)	8,49 (8,31 | 8,66)	-160 (-171 | -149)	0,0081 (-0,195 |0,211)	Dominant
	Probabilistic	1275 (1045 | 1504)	1113 (936 | 1290)	8,47 (7,95 | 8,99)	8,48 (7,96 | 9,00)	-162 (-239 | -84)	0,0098 (-0,193 | 0,212)	Dominant
FPM	Deterministic	579 (559 | 600)	504 (482 | 525)	8,19 (8,02 | 8,37)	8,21 (8,03 | 8,38)	-75 (-93 | -57)	0,0117 (-0,199 |0,223)	Dominant

Probabilistic	580 (502 | 657)	504 (432 | 577)	8,19 (7,67 | 8,71)	8,21 (7,69 | 8,72)	-75 (-136 | -15)	0,0138 (-0,197 | 0,225)	Dominant

Table 3 Deterministic and probabilistic results of melanoma, BCC and FPM cost-effectiveness analysis with credible intervals

Probabilistic results

All models show a slightly higher incremental QALY compared to the deterministic analysis as well as that they all stay dominant compared to usual care. The Incremental cost-effectiveness planes (figures 4-6) show the spread of the 10.000 model-iterations. The cost-effectiveness acceptability curves all show a constant probability between the 50% and 60% chance of cost effectiveness.

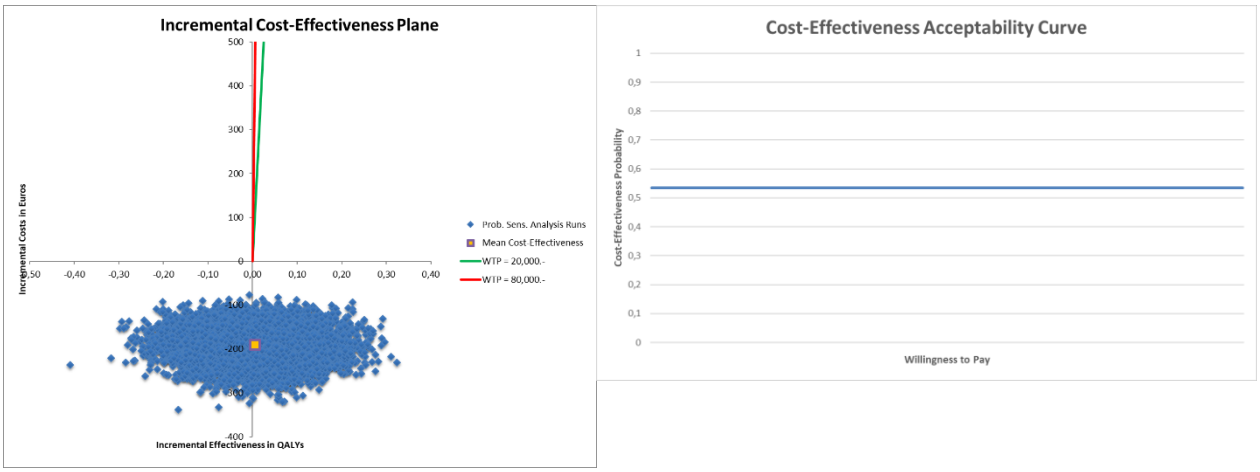

Figure 4 Incremental costs effectiveness plane with scatterplot of the 10.000 runs of the monte-carlo simulation of the melanoma model (left) and Cost-effectiveness acceptability curve of melanoma (right)

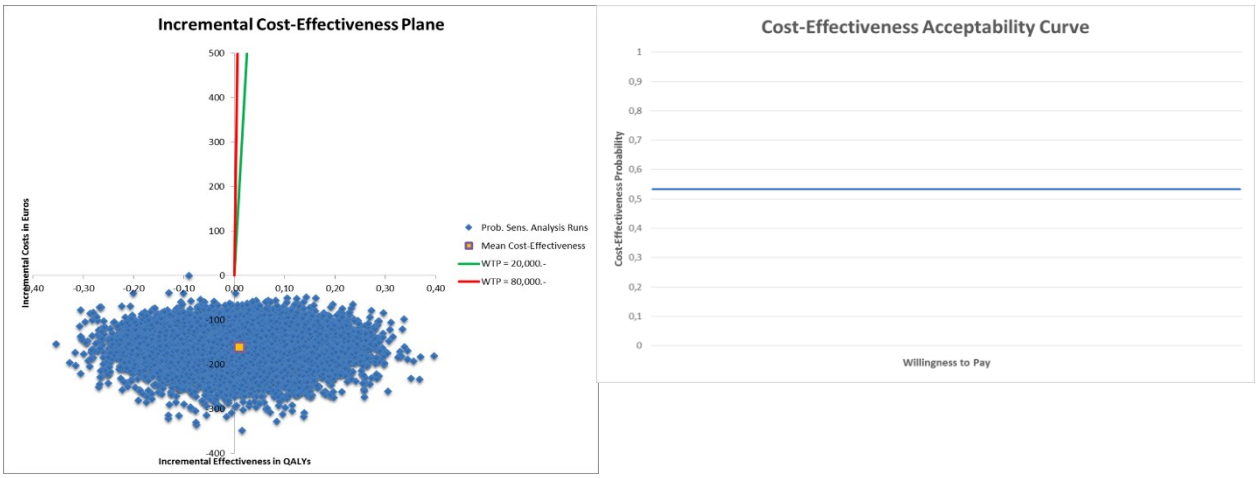

Figure 5 Incremental costs effectiveness plane with scatterplot of the 10.000 runs of the monte-carlo simulation of the BCC model (left) and Cost-effectiveness acceptability curve of BCC (right)

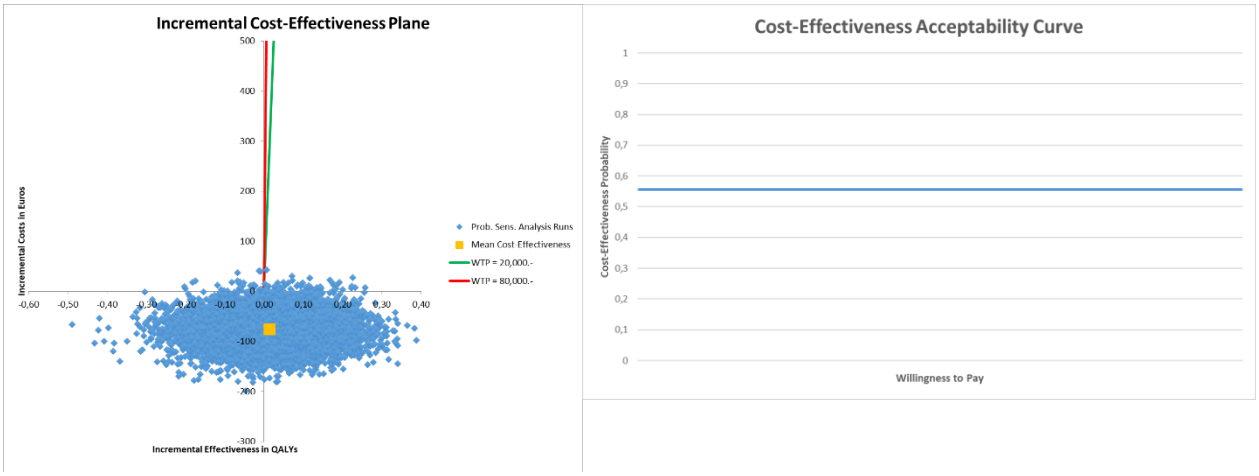

Figure 6 Incremental costs effectiveness plane with scatterplot of the 10.000 runs of the monte-carlo simulation of the FPM model (left) and Cost-effectiveness acceptability curve of FPM(right)

Sensitivity analysis

The sensitivity analysis shows that the melanoma model has a peak impact of just above 10.000 €/QALY and is most sensitive to differences in sensitivity, specificity, age and the costs of a diagnostic excision or RCM examination. There are negative peaks for both the 20% increase and decrease of sensitivity. The small peak is the 20% increase, causing less false negative diagnosis thereby increasing the QALY gain and reducing the ICER. The larger peak is caused by the incremental QALY dropping below 0 when the sensitivity is reduced by 20% to 0,74, turning the ICER negative

The analysis of the BCC model shows the biggest impact on the ICER of the model is made by adjusting the costs of biopsy and the general probability of skin cancer in the equivocal group. The least influential are the costs of a consult. However, all analyses showed dominance of the RCM pathway compared to usual care.

The analysis of the FPM model shows the biggest impact on the ICER of the model is made by adjusting the mean age, disutility of surgical treatment, probability that the equivocal lesion is malignant and the number of lesions per patient. The least influential are the costs of a consult, a therapeutic excision or the societal and family costs. As was the case in the previous model, all analyses showed dominance of the RCM pathway compared to usual care.

The subgroup analysis of head neck patients in the melanoma model shows an ICER dominance when all patients had lesions on their head and neck with an incremental QALY gain of 0,0115(Credible interval: -0,1577|0,1809) and costs equal to base case analysis. When all lesions were on the rest of the body the incremental QALY lowered to 0,00388 (-0,1646|0,1723). The BCC model showed no significant changes compared to the base case. The FPM model showed no significant chance when all lesions were in the head and neck area since the base-case already had 0,89 probability that the lesion would be there.

Decrease of this probability caused chances in QALY's, however is not likely and furthermore the model kept being dominant over usual care.

The scenario of equal sensitivity and specificity as biopsy or diagnostic excision yielded the following results. The melanoma model showed a significant increased incremental QALY (0,0143). The BCC and FPM model showed no significant changes compared to the base case.

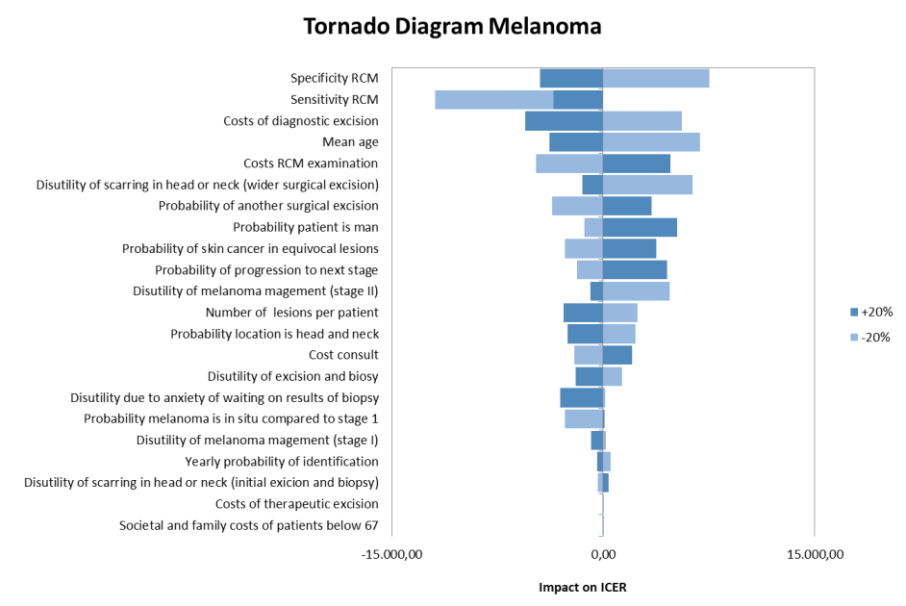

Figure 7 Tornado diagram of sensitivity analysis of melanoma model

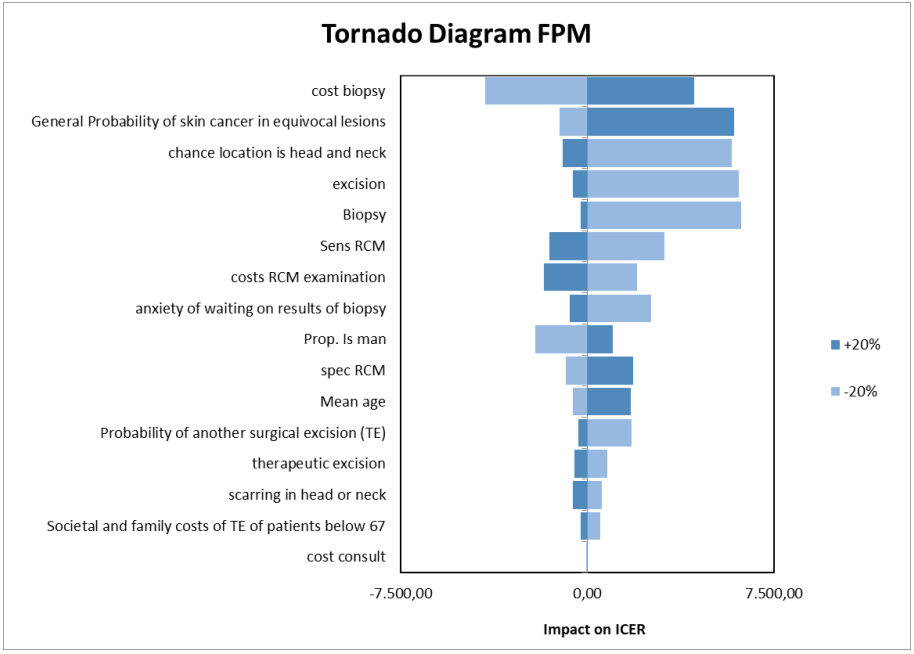

Figure 8 Tornado diagram of sensitivity analysis of FPM model

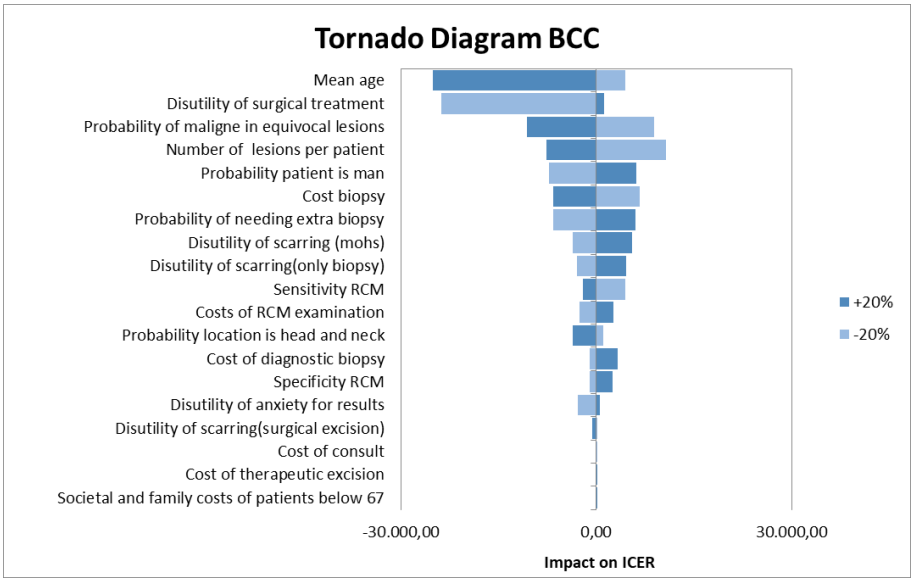

Figure 9 Tornado diagram of sensitivity analysis of BCC model

Discussion and conclusion

The models show marginal cost effectiveness of RCM compared to usual care. The QALY differences are minimal and the sensitivity analysis shows an almost equal chance of being not cost effective. The short term incremental QALY gain of the addition of RCM in the diagnostic pathway amount to only 0,1% of the accumulated QALY in the 15-year period. Therefore, the benefits of RCM in the short term are overpowered by the randomness of events in the next 15 years, causing the uncertainty in the model. So, there is no significant distinction to be made in cost-effectiveness between the two alternatives, however RCM can positively influence quality of care. The non-invasive character of RCM combined with the fast-track diagnostics yield enormous potential for better patient perception and satisfaction. This means benefits for institutions who value patient centered care.

The input of the model as well as the output is comparable with the cost effectiveness study by Edward et al[5] and effectiveness studies in literature[7–9]. The study conducted by Edwards et al. showed a ICER of 10.146 €/QALY. Due to the small differences in incremental QALY this can be deemed comparable. Their model estimated an incremental QALY of 0.009 in melanoma diagnosis and 0.011 in the BCC group compared to a respective 0,0045 and 0,0081 in this model. The differences in costs can be attributed to the differences between the UK and the Netherlands. The comparability of results and input parameters with current literature confirm the validity of the model and its outcome.

All assumption used in the model are based on expert opinion and/or literature. The most important assumptions are discussed below. The number of equivocal lesions examined each year, needed to calculate the costs per examination, is based on the retrospective cohort and assumed to be stable. Utility values were not measured due to retrospective nature of this study. Utility values are taken from

the review paper by Edwards et al. which in turn included papers from Sullivan et al., Tromme et al. and Seidler et al.[14–16] It is assumed that these utility values are representative for the Dutch population.

The eventual uptake and success of this new technique depends mostly on the implementation. For this to be a success a few things need to be considered. First, clear guidelines need to be drafted to control the patient flow since dermatologists indicated they would change their referral pattern in case RCM would be added to the diagnostic pathway.

The aim is to eventually substitute the majority of punch biopsies by RCM analysis. However, there is not enough evidence for all patient groups and the subtyping remains difficult, so clear guidelines are needed to manage and monitor this gradual change. Benefits of an increasing group of patients diagnosed using RCM are: lower costs per examination and knowledge gain to improve and optimize the RCM process.

Due to the mortality rate associated with melanoma, attention needs to be paid to conserve the current diagnostic sensitivity, as an increase of false negatives is not acceptable even with a significant increase in specificity by RCM. This could be accomplished by more extensive training, more experience and second opinions on the images. Another option is to create a high and low risk split within the equivocal group, with a mandatory follow-up for the high-risk patients after a negative RCM outcome. The assumption in this case would be that most false-negative patients would end up in the high-risk group and will be detected within 3 months after initial consult[6,20–22].

In the diagnosis of BCC, the most clinically relevant step is to determine the histological subtype to allow adequate treatment. A recent systematic review on the current diagnostic reference standard (i.e. punch biopsy) showed a sensitivity and specificity ranging from 61% to 85% and 79% to 88% respectively[23]. Research into BCC subtyping by RCM is still in its early stages and the knowledge into this subject is not sufficient for reliable decision making. Kadouch et al. showed the diagnostic accuracy of punch biopsy and RCM was comparable[24], but agreement of RCM in identifying the most aggressive subtypes ranged from 50% to 85% vs. 77% for punch biopsy[24,25]. This indicates the potential of RCM in subtyping of BCC, whilst also showing room for improvement.

In the diagnosis of LM dermoscopy has limited specificity as FPM can have overlapping diagnostic criteria. Once diagnosed LM is associated with problematic margin control due to subclinical spread, and subsequent high recurrence rates. RCM implementation could therefore not only prove useful in the diagnosis of LM, but also in the margin delineation before treatment. As the latter was not in the scope of this research, further research needs to be done to verify this application of the technology.

Strengths of this study are the number of patients included and their spread over the different types of skin malignancies. Moreover, this data was collected in a clinical setting and gives a good representation of the eventual implementation of RCM. Further research into subtyping of BCC, implementation of RCM in clinical practice, and capacity planning is needed. In the case of melanoma, an RCT into the effectiveness and cost effectiveness, comparable to an ongoing study for BCC[25], is recommended, including measurement of patient utility and to potentially identify high and low risk groups for false negative outcomes.

In conclusion, the addition of RCM to the diagnostic pathway of melanoma has comparable results to usual care when looking at QALY. Therefore, there is an almost even chance of cost-effectiveness of RCM. The new technique can become a valuable, and probably cost saving, option in the diagnostic process because of its non-invasiveness and fast-track diagnostics compared to current practice. These features can significantly boost patient centeredness, nevertheless further research is required to start substitution towards RCM.

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