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MELANOMA AND NON-INVASIVE IMAGING TECHNIQUES: STUDY OF TUMOR DYNAMICS AND COST-EFFECTIVENESS ESTIMATION IN TWO NATIONAL HEALTH SYSTEMS

MELANOMA E TÉCNICAS DE IMAGEM NÃO INVASIVAS: ESTUDO DA DINÂMICA TUMORAL E ESTIMATIVA DE CUSTO-EFETIVIDADE EM DOIS SISTEMAS NACIONAIS DE SAÚDE

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ABBREVIATION:

QALY - quality-adjusted life years

CEA - cost-effectiveness analysis

EAH – economic assessment in health

ICER - incremental cost-effectiveness ratio

PICO - patient or population, intervention, comparison, outcome

GDP - gross domestic product

DALY - disability-adjusted life years

UVR - ultraviolet radiation

LM - lentigo maligna

RCM - reflectance confocal microscopy

OCT - optical coherence tomography

PAK - pigmented actinic keratosis

NNE - number needed to excise

SSM - superficial spreading melanoma

NM - nodular melanoma

RGP - radial growth phase

MGP - microinvasive radial growth phase

VGP - vertical growth phase

DEJ - dermo-epidermal junction

BCCs - basal cell carcinomas

SD-OCT - spectral domain

HD-OCT - high-definition

D-OCT – dynamic optical coherence tomography

sBCC – superficial basal cell carcinoma

nsBCC – nonsuperficial basal cell carcinoma

SebK - seborrheic keratosis

UNIRIO - universidade federal do estado do rio de janeiro

UNIMORE - university of modena and reggio emilia

GP – general practitioner

MIS - in situ melanoma

SUS - sistema único de saúde, the brazilian public health system

SD - standard deviation

NMB - net monetary benefit

Incr Cost - incremental costs

EFF – effectiveness

Inc Eff - incremental effectiveness

ABSTRACT

Background: Melanoma is the cutaneous neoplasm with the worst prognosis. Despite adjuvant therapies, the prognosis of metastatic disease is limited and the costs with therapies are high. Thus, early stage diagnosis is crucial. Dermoscopy, reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) are non-invasive equipments available for skin cancer screening. Between these, only RCM allows the visualization of cells with a resolution close to histological analysis; thus it is useful for melanoma. It has been established the improvement in diagnostic accuracy when RCM is used secondarily to dermoscopy – increasing diagnosis of melanoma in early stages, reducing expenses with procedures in benign lesions and total expenses with chemotherapy required. Unfortunately, in Brazil the scenario is different: huge percentage of melanomas is classified in advanced stages and many interventions in benign lesions are performed - both contemplating for high expenses for the health system.

Objectives: To study the application and validity of advanced non-invasive methods in Brazil to obtain clinical information useful for the clinical management of the patient with melanoma, and analyse the cost-effectiveness of RCM in Brazil.

Material and methods: First part (in the University of Modena and Reggio Emilia, Italy (UNIMORE)). Studies on the applicability and benefits of RCM and OCT, including the evaluation of benefits about evolution of the OCT system (Dynamic-OCT; D-OCT), which provides microangiographic images of the skin. Vascular characteristics were correlated to different skin conditions, especially skin cancer. In melanomas there was a correlation between tumor thickness and D-OCT aspects. As the department of Dermatology of UNIMORE is recognized by its efficiency in diagnosing skin cancer (especially melanoma), a comparison between this approach and Brazil situation was done, in order to compare diagnostic accuracy and its socio-economic consequences. All melanomas diagnosed in the

department of Dermatology of UNIMORE from 2009 until 2018 were included in the study, being allocated according to the time of diagnosis - before or after the introduction of RCM in Modena: Modena model 1 (from 2009 to 2011 – without RCM) and Modena model 2 (from 2012 to 2018 – with RCM). In Brazil melanoma are subnotified, thus data were provided by the largest study in melanoma in the country, in 2018. All cases were classified according to TNM stages (0, I, II, III and IV) for comparison. Internal comparison between Modena models (1 vs 2) was also done.

Second part (in the Universidade Federal do Estado do Rio de Janeiro, Brazil (UNIRIO)). To better identify the differences and transversalities in the systems (Modena vs Brazil) and its repercussions in the amount of melanomas diagnosed in early or advanced stages, a cost-effectiveness evaluation was structured based on a static mathematical model - the decision tree - because of its simplicity and the time available for the conclusion of the study. All analysis and graphics were performed with the aid of TreeAge Pro® 2019 software. The decision tree represented 2 scenarios (reference scenario – using only dermoscopy; and alternative scenario – using also RCM) based on 2 decision nodes (dermoscopy and RCM), each representing one scenario and mutually excluders for the diagnosis of melanoma; each of them presented 6 chance nodes. For decision tree, stages were grouped and classified according to TNM as follows: *early stages* (0, I and II) and *advanced stages* (III and IV), which corresponded to early or late diagnosis, respectivelly. Regardless of the time of diagnosis (early or late), it was considered the patient could be treated or not (with or without treatment). Finally, whether patient is treated or not, he could whether (a) survive and die from other causes, or (b) progress to metastasis and die as a result of disease progression. Since the model is not dynamic, there is no possibility for the patient to transit through other possible health states following the natural history of melanoma. In the composition of costs for diagnosis and treatment of melanoma, we estimated prices of inputs, drugs and medical

honoraria using the macrofinancing technique, which considers a total cost a “package” of services.

Results: First part (UNIMORE) – Comparison between both Modena models (1 vs 2) showed higher percentage of stage 0 in Modena model 2 (40.3% vs 28.8%), and a reduction in the percentage of stages III/IV in almost 50% (13.9% in Modena model 1 vs 7.5% in Modena model 2). Comparison between Brazil and Modena model 1 demonstrated much higher percentages of melanomas diagnosed in advanced stages in Brazil, with even more discrepancy when compared with model 2 (46.7% vs 19.5% and 12.6%, respectively).

Second part (UNIRIO) – Roll back evaluation of the decision tree showed an estimated incremental cost-effectiveness ratio of R$ 3,966.10 – meaning that in order to obtain one more unit of effectiveness this value would have to be disbursed, which is within the willingness to pay threshold of the model. Net monetary benefit (NMB) showed a positive value of R$ 1,894.28 for RCM examination, what means that each patient diagnosed and treated early will enable a return on invested capital in the order of the NMB. Unlike in dermoscopy NMB showed a negative value (- R$ 6,596.07), which means loss of resource. The cost-effectiveness plan showed that the dominance of confocal microscopy is not absolute in relation to dermoscopy. Expected values of both, incremental cost-effectiveness ratio and NMB were not sensitive to parametric variations which attests the robustness of the model and the confidence in its results.

Limitations: Dynamic models would be the most appropriate to analyze the costs and consequences of treating a melanoma patient. A limitation of this study is in fact to do not have taken into account the probabilities defined by the natural history of the disease, the effect of skin cancer screening, the effectiveness of the treatment in different clinical stages, the risks of complications, the competitive risks of mortality and the loss of income from death or morbidity, which are not possible to consider in the static decision tree model.

Conclusion: Modena model 2 shows that the best efficacy is in the combined use "dermoscopy + RCM". Brazilian system would require relevant interventions, both toward promoting awareness campains and getting dermatologists to be better trained in dermoscopy. Cost-effectiviness analysis also demonstrated the incorporation of RCM in Brazil would result cost-effective for the Brazilian Health System.

ESTRATTO

Introduzione: Il melanoma è la neoplasia cutanea con la prognosi peggiore. Nonostante le terapie attualmente disponibili, la prognosi della malattia metastatica rimane non ottimale mentre i costi sono estremamente elevati. Pertanto, la diagnosi nella fase iniziale è cruciale, permettendo la tempestiva rimozione della patologia in fasi in cui il rischio di progressione è estremamente basso. Dermoscopia, microscopia confocale a riflettanza (RCM) e tomografia a coerenza ottica (OCT) sono apparecchiature non invasive disponibili per lo screening e lo studio del cancro della pelle. Tra questi, la RCM consente la visualizzazione di cellule ad una risoluzione vicina all'analisi istologica, offrendo la miglior accuratezza diagnostica per il melanoma. Il miglioramento dell'accuratezza diagnostica in RCM utilizzato dopo screening dermatoscopio ha portato ad un aumento della diagnosi di melanoma in fase iniziale, riducendo la spesa sanitaria derivata da procedure chirurgiche di lesioni benigne, oltre che ad un potenziale decremento delle spese di terapia relative al melanoma avanzato. Sfortunatamente in Brasile lo scenario è diverso: un enorme percentuale di melanomi è diagnosticato in stadi avanzati, e inoltre un alto numero di interventi è eseguito per rimuovere lesioni benigne, entrambe le situazioni generando un eccesso di spesa per il sistema sanitario.

Obbietivi: Studiare l'applicazione e la validità dei metodi avanzati non invasivi per la diagnosi di melanoma, e verificare attraverso modelli di farmaco-economia la applicabilità in Brasile.

Materiali e metodi: Prima parte (all'Università di Modena e Reggio Emilia, Italia (UNIMORE)). Studi sull'applicabilità e benefici di RCM e OCT, inclusa la valutazione dei benefici sull'evoluzione del sistema OCT (Dynamic-OCT; D-OCT), che fornisce immagini microangiografiche della pelle. Le caratteristiche vascolari sono risultate correlate alla aggressività biologica del tumore. Nei melanomi è stata osservata una correlazione tra lo spessore del tumore e gli aspetti D-OCT. Mentre gli studi incentrati su RCM hanno

confermato non solo la elevata accuratezza diagnostica, ma anche la applicabilità in lesioni di difficile diagnosi dermoscopica attraverso la identificazione di una ridotta serie di parametri, facili da individuare anche da operatori con limitata esperienza.

Seconda parte (all'Universidade Federal do Estado do Rio de Janeiro, Brasile (UNIRIO)). Poiché la Clinica Dermatologica di UNIMORE è riconosciuta per la sua competenza ed efficacia organizzativa nella diagnosi dei tumori cutanei, è stato confrontato il risultato raggiunto presso di essa in un arco di 10 anni in cui sono avvenuti la revisione dei percorsi di accesso e l'introduzione sistematica della RCM, con la situazione del Brasile, al fine di verificare la convenienza e le conseguenze socio-economiche in caso di trasferimento dello stesso sistema in un differente contesto geografico, epidemiologico e socio-economico. Tutti i melanomi diagnosticati nella Clinica Dermatologica di UNIMORE dal 2009 al 2018 sono stati considerati nello studio, assegnati in base al momento della diagnosi - prima o dopo l'introduzione di RCM, distinguendo così due differenti modelli diagnostici, precisamente il modello Modena-1 (dal 2009 al 2011 - senza RCM) e modello Modena-2 (dal 2012 al 2018 - con RCM). In Brasile il melanoma è sottonotificato, quindi i dati sono stati ottenuti dall'analisi del maggior studio epidemiologico sul melanoma nel Paese, datato nel 2018. Tutti i casi sono stati classificati in base allo stadio TNM-AJCC (0, I, II, III e IV) per il confronto. È stato anche effettuato un confronto interno tra i modelli di Modena (1 vs 2). Per identificare meglio le differenze e le trasversalità nei sistemi (Modena vs Brasile) e le sue ripercussioni sulla quantità di melanomi diagnosticati in fasi iniziali o avanzate, una valutazione del rapporto costo-efficacia è stata strutturata sulla base di un modello matematico statico - l'albero decisionale con l'aiuto del software TreeAge Pro® 2019, rappresentando 2 scenari (scenario di riferimento - usando solo la dermoscopia; e scenario alternativo - usando anche RCM) e basato su 2 nodi di decisione (dermoscopia e RCM). Nella composizione dei costi per la diagnosi ed il trattamento del melanoma, abbiamo stimato i prezzi di input, farmaci ed

onorari medici utilizzando la tecnica di macrofinanziamento, che considera come costo totale un "pacchetto" di servizi.

Risultati: Il confronto tra i due modelli di Modena (1 vs 2) ha dimostrato una percentuale più alta di melanomi allo stadio 0 nel modello 2 di Modena (40.3% vs 28.8%) ed una riduzione della percentuale di melanomi in stadio fasi III / IV in quasi 50% (13.9% nel modello 1 di Modena vs il 7.5% nel modello 2 di Modena). Il confronto tra Brasile ed il modello 1 di Modena ha dimostrato percentuali molto più elevate di melanomi diagnosticati in stadi avanzati in Brasile, con una discrepanza ancora più evidente quando veniva confrontato rispetto al modello 2 (46.7% vs 19.5% e 12.6%, rispettivamente). La valutazione di rollback dell'albero decisionale ha dimostrato un rapporto costo-efficacia incrementale stimato di R$ 3.966,10, valore abbondantemente entro la soglia di "volontà di pagare" attualmente considerata in Brasile. Il beneficio monetario netto (BMN) ha mostrato un valore positivo di R$ 1.894,28 per l'esame RCM, che significa che ogni paziente diagnosticato e trattato in anticipo consentirà tale ritorno sul capitale investito. Viceversa la dermoscopia mostrava un BMN negativo, implicando un costo aggiuntivo per il sistema, in quanto il miglioramento della accuratezza diagnostica veniva controbilanciato da un eccesso di asportazioni di lesioni benigne. Il modello di costo-efficacia comunque ha dimostrato che sia RCM che dermoscopia sono metodiche valide ed economicamente convenienti per la diagnosi di melanoma.
Limitazioni: Una limitazione di questo studio è di non aver preso in considerazione le probabilità definite dalla storia naturale della malattia, l'effetto dello screening del cancro cutaneo, l'efficacia del trattamento nelle diverse fasi cliniche, i rischi di complicazioni, i rischi competitivi di mortalità e perdita di reddito per morte o morbilità.

Conclusione: Il modello 2 di Modena mostra che la migliore efficacia è nell'uso combinato "dermoscopia + RCM". Il sistema brasiliano richiederebbe interventi pertinenti, sia per promuovere campagne di sensibilizzazione e modalità di accesso al paziente, sia per ottenere

una migliore formazione in dermoscopia da parte dei dermatologi. L'analisi costo-efficacia ha anche dimostrato che l'introduzione di RCM in Brasile risulterebbe conveniente per il sistema sanitario brasiliano.

ABSTRACT (Portughese version):

Introdução: Melanoma é a neoplasia cutânea de pior prognóstico. Apesar das terapias adjuvantes, o prognóstico da doença metastática é limitado e os custos são altos. Portanto, o diagnóstico em estágio inicial é crucial. A dermatoscopia, a microscopia confocal de reflexão (RCM) e a tomografia de coerência óptica (OCT) são equipamentos não invasivos disponíveis para o rastreamento do câncer de pele. Entre estes, apenas RCM permite a visualização de células com resolução próxima à análise histológica; portanto, é útil para melanoma. Foi reconhecida a melhora na precisão diagnóstica quando RCM é utilizado secundariamente à dermatoscopia - aumentando o diagnóstico de melanoma nos estágios iniciais, reduzindo as despesas com procedimentos em lesões benignas e as despesas totais com quimioterapia. Infelizmente, no Brasil, o cenário é diferente: um grande percentual de melanomas é classificado em estágios avançados e muitas lesões benignas são abordadas cirurgicamente - ambos contribuindo com altos gastos para o sistema de saúde.

Objetivos: Estudar a aplicação e a validação destes métodos não invasivos no Brasil a fim de obter informações clínicas úteis ao manejo clínico do paciente com melanoma, e analisar o custo-efetividade da RCM no Brasil.

Materiais e métodos: Primeira parte (na Universidade de Modena e Reggio Emilia, Itália (UNIMORE)). Estudos sobre a aplicabilidade e os benefícios da RCM e da OCT, incluindo a avaliação dos benefícios na evolução do sistema de OCT (Dynamic-OCT; D-OCT), que fornece imagens microangiográficas da pele. As características vasculares foram correlacionadas em diferentes condições cutâneas, principalmente no câncer de pele. Com relação ao melanoma, houve uma correlação entre a espessura do tumor e os aspectos vasculares na D-OCT. Como o departamento de Dermatologia da UNIMORE é reconhecido por sua eficiência no diagnóstico do câncer de pele (principalmente melanoma), foi realizada uma comparação entre a realidade italiana (UNIMORE) e a situação brasileira, a fim de

comparar a precisão do diagnóstico e suas consequências socioeconômicas. Todos os melanomas diagnosticados no departamento de Dermatologia do UNIMORE de 2009 a 2018 foram incluídos no estudo, sendo alocados de acordo com o momento do diagnóstico - antes ou após a introdução da RCM em Modena: Modena modelo 1 (de 2009 a 2011 - sem RCM) e Modena modelo 2 (de 2012 a 2018 - com RCM). No Brasil sendo o melanoma subnotificado, os dados utilizados foram os fornecidos pelo maior estudo em melanoma no país, em 2018. Todos os casos foram classificados de acordo com o estadiamento TNM (0, I, II, III e IV) para comparação. Também foi feita uma comparação interna entre os modelos de Modena (1 vs 2).

Segunda parte (na Universidade Federal do Estado do Rio de Janeiro, Brasil (UNIRIO)). Para melhor identificar as diferenças e transversalidades nos sistemas (Modena vs Brasil) e suas repercussões na quantidade de melanomas diagnosticados em estágios iniciais ou avançados, uma avaliação de custo-efetividade foi estruturada com base em um modelo matemático estático - a árvore de decisão - devido a sua simplicidade e o tempo disponível para a conclusão do estudo. Todas as análises e gráficos foram realizados com auxílio do software TreeAge Pro® 2019. A árvore de decisão representou 2 cenários (cenário de referência - usando apenas dermatoscopia; e cenário alternativo - usando também RCM) com base em 2 nós de decisão (dermatoscopia e RCM), cada um representando um cenário e sendo excludentes mutuamente para o diagnóstico de melanoma; cada um deles apresentou 6 nós de chance. Para a árvore de decisão, os estágios foram agrupados e classificados de acordo com TNM, como segue: estágios iniciais (0, I e II) e avançados (III e IV), que correspondiam ao diagnóstico precoce ou tardio, respectivamente. Independentemente do tempo do diagnóstico (precoce ou tardio), considerou-se que o paciente poderia ser tratado ou não (com ou sem tratamento). Finalmente, se o paciente é tratado ou não, ele pode (a) sobreviver e morrer de outras causas, ou (b) progredir para metástase e morrer como resultado da progressão da

doença. Como o modelo não é dinâmico, não há possibilidade do paciente transitar por outros possíveis estados de saúde, seguindo a história natural do melanoma. Na composição dos custos para diagnóstico e tratamento do melanoma, estimamos preços de insumos, medicamentos e honorários médicos usando a técnica de macrofinanciamento, que considera para custo total um "pacote" de serviços.

Resultados: Primeira parte (UNIMORE) - A comparação entre os dois modelos de Modena (1 vs 2) mostrou maior percentual de estágio 0 no modelo 2 de Modena (40.3% vs 28.8%) e uma redução no percentual dos estágios III / IV em quase 50% (13.9% no modelo 1 de Modena vs 7.5% no modelo 2 de Modena). A comparação entre Brasil e o modelo 1 de Modena demonstrou percentuais muito mais altos de melanomas diagnosticados em estágios avançados no Brasil, com discrepância ainda maior quando comparado ao modelo 2 (46.7% vs 19.5% e 12.6%, respectivamente).

Segunda parte (UNIRIO) - A avaliação da árvore de decisão demonstrou uma relação custo-benefício incremental estimada de R$ 3.966,10 - o que significa que, para obter mais uma unidade de eficácia, esse valor teria que ser desembolsado, o que está dentro do limiar de disposição para pagar. O benefício monetário líquido (BML) apresentou um valor positivo de R$ 1.894,28 para o exame RCM, o que significa que cada paciente diagnosticado e tratado precocemente permitirá um retorno sobre o capital investido na ordem do BML. Diversamente, na dermatoscopia o BML apresentou um valor negativo (- R$ 6.596,07), o que significa perda de recursos. O plano de custo-efetividade mostrou que a dominância da microscopia confocal não é absoluta em relação à dermatoscopia. Os valores esperados de ambos, relação de custo-efetividade incremental e BML, não foram sensíveis a variações paramétricas atestando a robustez do modelo e a confiança em seus resultados.

Limitações: Modelos dinâmicos seriam os mais apropriados para analisar os custos e as consequências do tratamento de um paciente com melanoma. Uma limitação deste estudo é,

de fato, não levar em consideração as probabilidades definidas pela história natural da doença, o efeito do rastreamento do câncer de pele, a eficácia do tratamento em diferentes estágios clínicos, os riscos de complicações, os riscos de mortalidade e perda de renda por morte ou morbidade, que não são possíveis de serem considerados no modelo estático de árvore de decisão.

Conclusão: O modelo 2 de Modena mostra que a melhor eficácia está no uso combinado "dermatoscopia + RCM". O sistema brasileiro necessita de intervenções relevantes, tanto na promoção de campanhas de conscientização quanto na capacitação dos dermatologistas em dermatoscopia. A análise de custo-efetividade também demonstrou que a incorporação da RCM no Brasil resultaria rentável para o Sistema de Saúde Brasileiro.

1. INTRODUCTION:

I. MELANOMA SCENARIO

Skin cancers are divided into melanoma and non-melanoma (basal cell carcinoma, squamous cell carcinoma). The non-melanoma type is the most frequent cancer in Brazil, corresponding to 30% of all malignant tumors registered in the country, and presents high cure rates if diagnosed and treated early. An estimation of 165,580 new cases of non-melanoma skin cancer has been made for the year 2018 in Brazil.[a]

Most melanomas (70%) develop in normal skin (melanoma de novo) while 30% come from pre-existing melanocytic nevi.[1] Intermittent sun exposure, light skin and eyes, photodamage, presence of atypical nevi or large amount of common nevi (> 50), history of personal skin cancer (melanoma or non-melanoma), personal and/or family history of melanoma are risk factors for melanoma development.

Melanoma is the cutaneous neoplasm with the worst prognosis. Although it accounts for less than 5% of all skin cancers, it is responsible for 95% of deaths[2] because of its high potential for metastasis and high lethality.

According to Gershenwald and Scolyer the 5-year survival rates vary from 93-69% for stage IIIA-stage IIIC melanoma, compared to 99-97% for stage IA–IB and 94-87% for stage IIA-IIB melanoma. Alike, 10-year survival rates decrease from 88% for stage IIIA to 69% for stage IIIC melanoma.[3]

According to Balch et al, among patients with metastatic melanoma, stage IV, the estimated mean survival time is around 8 months, and only 10% survive 5 years from diagnosis.[4] Thus, early diagnosis followed by prompt complete surgical excision is crucial for survival and better prognosis / survival rate.

[a] http://www2.inca.gov.br/wps/wcm/connect/inca/portal/home

Despite advances in metastatic melanoma treatments, with the introduction of target and immuno-therapies, the success of the therapy in advanced melanoma remains limited and the prognosis of metastatic disease is restricted. [5]

Adjuvant therapy with interferon-α was offered to patients with stage II and III melanoma, whereas in cases of distant metastasis without possibility of surgical therapy, systemic treatment is indicated.[6] In US and in Europe target therapies and immunotherapies are also proposed for stage IIIB patients, showing relevant disease free and overall survival rates. [7,8]

However, due to the limited resources given in the Brazilian public health system, the access to the new drugs is not given for advanced nor for adjuvant treatments, because of the high cost per patient.[9] The traditional chemotherapy, based on the use of dacarbazine, represents the standard of care for advanced melanoma in Brazil. Even if the cost is limited, it does not provide satisfactory disease free and overall survival rates, and its efficacy is far below the one granted by the new, but expensive, treatments. In addition, melanoma is historically known to be resistant to radiotherapy when compared to other types of cancer[10], further limiting the treatment portfolio for advanced disease. Concerns about the economic sustainability of health systems have been a subject of intense discussion at both government and academic levels, given the growing demand for health services as opposed to scarcity of resources.

The increasingly use of expensive technologies is a major cause of rising health costs, pointing to the need to use information on the costs and benefits of health interventions to assist in setting priorities for allocation of resources[11].

The economic analysis of health technologies, or as it is better known, as the Economic Health Assessment (EHA) is a formal analytical technique to compare different proposed alternatives, taking into account the costs of resources applied and the consequences obtained

in terms of health. Thus, helping with decisions about prioritizing interventions and allocating resources.[b] Every EHA has as its starting point a research question or guiding question. This question will help to determine the scope, research design, and the most appropriate technique.[b] The acronym PICO (*patient or population, intervention, comparison and outcomes*) is often used to identify important points of the research question and to guide the search strategy.[b]

Since the cost of new treatments in melanoma is evidently not effordable in Brazil, and also it is able to cure a limited proportion of patients with advanced disease, our research question focused on the effects generated from the improvement of early diagnosis, with a promoted and systematic use of technologies.

Based on the acronym PICO, the research question followed the following structure:

P = Individuals with suspected skin cancer;

I = reflectance confocal microscopy;

C = dermoscopy;

O = early diagnosis and treatment.

According to the Ministry of Health's Economic Analysis Guideline, economic analyzes may be partial or complete. In the partial, the report includes the description or analysis of costs and may contain information on the performance of a particular technology, and there is no comparison of costs and health consequences between two or more alternatives.[b] While in complete (or total), there is a comparison of costs and some measure of performance of the alternatives considered. They are: a) cost-minimization; b) cost-utility; c) cost-benefit and d) cost-effectiveness, as described below. Considering the fact that this research opts for the Economic Cost-Effectiveness Analysis, this type will be approached in more detail.

[b] http://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf

• Cost-Minimization: Type of study in which the objective is to identify the least expensive way to achieve the desired outcome and is used when there is strong evidence that two or more health interventions have the same outcome [b]

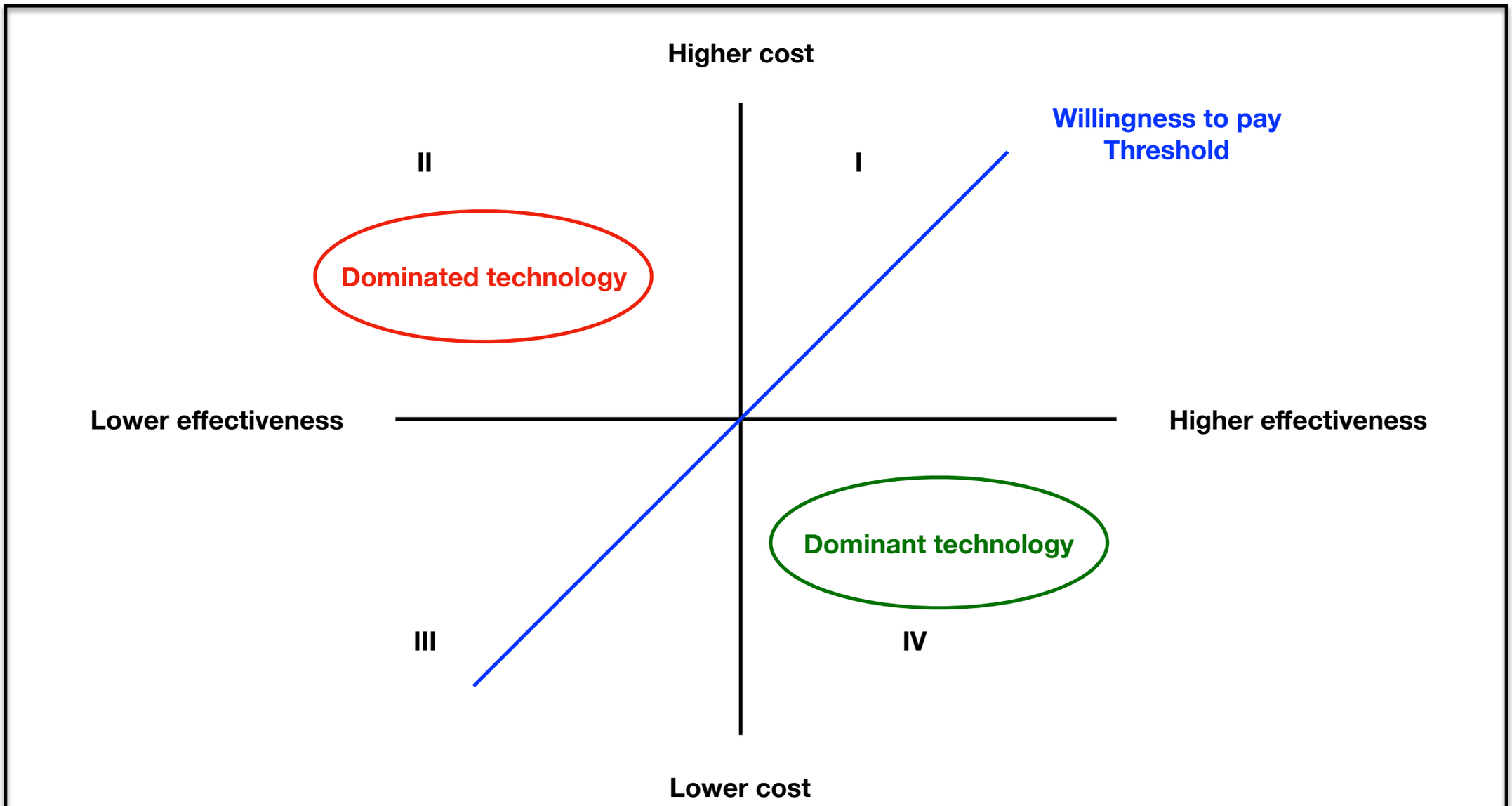
• Cost-utility: Outcome is measured in quality-adjusted life years (QALY), in objective and / or subjective terms, combining quality and quantity of life in outcome measurement [b]

• Cost benefit: The costs and consequences of interventions are measured in monetary units, allowing also a comparison not only between health interventions, but also among other decision areas [b]

• Cost effectiveness: Cost-Effectiveness Analysis (CEA) is a synthesis methodology in which costs are confronted with clinical outcomes, whose objective is to evaluate the impact of different alternatives that aim to identify them with better treatment effects, usually in exchange for lower cost, seeking to fill the gap between preferences (subjectivity) and science (objectivity, validity, reproducibility). [12]

It is the most commonly used method in Economic Assessment in Health (EAH), where costs are measured in monetary units, and outcomes (health consequences) are measured in non-monetary units (eg, prevented deaths, life years gained, among others) [b]

In CEA comparable alternatives can be placed on a cost-effectiveness plan, which consists of a graphical representation of a Cartesian plane, where the intersection of *x* and *y* axes indicates the origin of costs and effectiveness for the standard comparison factor. When a technology or intervention is more effective and cheaper it dominates the scenario (quadrant IV) differently from quadrant II that is less effective and more expensive. In quadrant I (where technology is more expensive and more effective), a scenario often encountered, and in quadrant III (where technology is cheaper and less effective) there is no clarity in dominance. In this case, the incremental cost-effectiveness ratio (ICER) and the willingness to pay threshold (WTP) will need to be considered.[13] (**Figure 1**).



Source: adapted from Secoli et al. (2010) and Vanni et al. (2009).

Figure 1: Cost-effectiveness plan. In quadrant I, technology is more expensive and more effective; in quadrant II, technology is less effective and more expensive; in quadrant III, technology is cheaper and less effective; and in quadrant IV technology is more effective and cheaper.

After calculating the costs and effectiveness of the strategies, they should be ordered from lowest to highest cost. Then, calculate the incremental cost-effectiveness ratio, always comparing each strategy with the immediately less expensive one:

ICER = (cost of intervention X - cost of intervention Y) / (effectiveness of intervention X - effectiveness of intervention Y).

The decision to choose the new intervention depends on how much society is willing to pay for this additional health gain. Therefore, any new intervention that lies to the right of the threshold in the cost-effectiveness plan is considered cost-effective and should be adopted as it represents a better use of resources compared to the current intervention.[13]

How to Design the Research Question:

The research problem or question is a s*ine qua non* condition for guiding an EAH. For this, the question must follow its own method for guidance purposes, determination of the research object, as well as selection of the most appropriate type of analysis to be used.

First, available technologies and their efficacy and applicability are considered. Secondly, the PICO method is applied to define the research problem and its main actors. Then, a decision model is chosen. Decision model is any mathematical structure that proposes to represent health and economic outcomes of patients or populations in varied scenarios, aiming to represent the real world complexity in a more understandable way, and simplifying the analysis of complex problems.[14]

Between existing decision models, the decision tree is the most suitable in this research because it represents clinical and epidemiological problems, has a direct relationship with short-term outcomes, and is the simplest form of decision models used routinely. It is also valued for its transparency and excellent ability to describe alternative options.[15]

The first point of the tree, the decision node (a square) represents the decision question, usually with two options represented. The paths that follow each option represent a series of

logically ordered alternate events, denoted by branches emanating from random nodes (the circles). The alternatives at each chance node must be mutually exclusive and their probabilities must be exactly one. The end point of each route is indicated by terminal nodes (triangles) in which the values or benefits are attributed. [16]

By opting for one of these perspectives, the scope of cost estimation is restricted to what is effectively the financial responsibility of the selected payer. Taking SUS as a reference, only the inputs made available by it are included in the analysis. According to Silva, Silva and Pereira[17], direct cost estimatives can be obtained through micro-costing and macro-costing methods. The micro-costing methods correspond to aggregate components. Thus, it reflects the characteristics of the sample whose degree of generalization is lower, being the best option for more complex services and when human resources have greater weight. [b]

Cost estimates must be presented for a given year, and must be adjusted over time. Therefore, the costs that will be incurred in the future should apply a discount rate to bring them to present value, recommending the rate of 5% per year from the second year.

Since 2001 the World Health Organization, through the Report of the Commission on Macroeconomics and Health, [18] taking into account the Gross Domestic Product (GDP) per capita and the estimated value of the years Disability-Adjusted Life Years (DALY) recommends as an explicit threshold for willingness to pay to avoid 1 DALY: (a) technologies costing less than 1 GDP per capita would be considered very cost-effective; (b) technologies costing up to 3 GDP per capita would be considered cost-effective; and (c) technologies costing more than 3 GDP per capita would not be considered cost-effective.

Scenario in Brazil

Geographically it is known that the incidence of ultraviolet radiation (UVR) is inversely proportional to the latitude of the site; so, the lower the latitude, the higher is the UVR

incidence. Brazil is a large country lying between latitude 5°16'20 "(in Monte Caburaí - Roraima) and 33°45'03" (in Arroio Chuí – Rio Grande do Sul), and it presents 92% of its extention located in the intertropical zone. The country also has a vast seacost, which is an incentive to the sun exposure throughout the whole year. Although intermittent sun exposure is the main villain in the physiopathology of cutaneous melanoma, chronic / continuous sun exposure is responsible for the solar type of melanoma (lentigo maligna (LM)).

Regarding ethnicity, Brazil is richly mixed. Even if it is not a country mainly composed by light skin population and clear eyes, it is possible to notice an important European influence. Between the years 1870 and 1953 almost five million imigrants moved to Brazil. Most of them were originally from Italy and Portugal, but also from Germany, Spain and Japan. At that time imigrants chose the South and Southeast regions of Brazil to inhabit – which are the most populous regions of Brazil, concentrating 56.6% of Brazilian population and 80% of melanomas in the country. [19]

The National Committee On Incorporating Technologies In The Single Health System in Brazil revealed that the estimated number of new cases of cutaneous melanoma between 2012 and 2013 in Brazil was 6.230 cases (3.170 among men and 3.060 among women). Data from hospital-based cancer registries (System for Hospital Registry of Cancer - Public Tabulator and Oncocentro Foundation in São Paulo - Hospital Registry of Cancer) show that 19% of the cases with reporting of tumoral staging were classified as stage III. [20]

An estimation of 6.260 new cases of melanoma with 1.794 deaths has been made for the year 2018 in Brazil.[c]

Although melanoma and other skin cancers histologically proven should be notified and registered as any other tumor is, unforfortunately in Brazil there is a remarkable subnotification of these cases, echoing to falsely less quantity than reality.

[c] https://www.inca.gov.br/tipos-de-cancer/cancer-de-pele-melanoma

II. AVAILABLE AND ADVANCED DIAGNOSTIC TECHNOLOGIES:

Regarding the techniques which add information and subsequntely enhance the clinical and early diagnosis of skin cancer, there are nowadays dermoscopy and reflectance confocal microscopy (RCM), whereas optical coherence tomography may help to define other tumor characteristics (OCT).

Dermoscopy, also known as dermatoscopy, is a noninvasive diagnostic technique that magnifies the skin enabling the visualization of the sub-surface structures of it, and has been shown to be cost-effective in the diagnosis of melanoma and non-melanoma skin cancers,[21] and to enhance the diagnostic accuracy of melanomas when performed by experienced professionals.[22,23,24] This technique has successfully been introduced in routine screening for skin cancer, and nowadays shows widespread clinical use, [25] also thanks to its handiness, portability, numerous and widespread training opportunities, and very low cost.

Reflectance confocal microscopy is a noninvasive novel technique that allows the visualization of cells and skin structures in real time with resolution close to histological analysis. [26] It is an optical imaging technique that uses the diode laser as a coherent monochromatic light source, which penetrates the tissue and illuminates a specific single point. The light from the stimulated section is reflected through a filter and forms the image on the detector. This filter allows the selective excitation of a particular point at which the focus is reached and rejects the reflection of the out-of-focus area, thus obtaining a "confocal" image.

In dermatology, this technique is applied both in clinical settings and research. It is the only in vivo technique that allows horizontal visualization of the skin up to the superficial dermis (approximately 250 μm) with a cellular level resolution (0.5-1.0 μm in the lateral dimension and 4.0-5.0 μm in the axial dimension), [27] being a reliable bridge between dermoscopy and histopathology examination. [28,29] Even if histology is the gold standard

evaluation for the definitive diagnosis of melanoma, RCM has been reported as a tool to possibly enhance the accuracy of histopathologic diagnosis. [30]

RCM has been shown to be especially valuable for in vivo evaluations of melanocytic lesions, since melanin and melanosomes are powerful sources of contrast allowing the individualization of melanocytic cells. [31] Besides the evaluation of melanocytic lesions, RCM is also valuable for the diagnosis of other cutaneous tumors, such as squamous cell carcinoma[32,33,34] and basal cell carcinoma. [35,36]

Even in the hands of masters in dermoscopy, it is not rare to find benign lesions with dermatoscopic features indistinguishable from melanomas, as well as melanomas still without specific dermatoscopic characteristics. [37,38] For this reason, in some developed countries where the Health System focus on the early diagnosis and improvement of diagnostic accuracy of skin cancer (mostly in Europe, Australia and in some advanced centers in US) RCM is already applied in combination to dermoscopy in cases of doubtful lesions. It results in the improvement of diagnostic confidence and accuracy, and frequently leads to management changes. [39,40,41,42,43,44] Classically, hypopigmented lesions represent a challenge for diagnosis. These hypopigmented or even amelanotic lesions benefit a lot from RCM evaluation since cellular evaluation will detect modifications as well as in pigmented lesions.[45,46,47]

RCM is also an interesting method for monitoring skin lesions over time and reducing unnecessary surgical excisions, such as in patients with multiple atypical nevi. [48]

Lentigo maligno, solar melanoma located on the face / head, is considered a diagnostic challenge because it presents clinical and dermoscopic features similar to non-malignant pigmented lesions, such as solar lentigo and pigmented actinic keratosis (PAK). In addition to the increasing on the diagnostic specificity, [49,50,51,52] RCM also allows the definition of the margins of LM with great accuracy (pre-surgical mapping) [53,54,55] which may reduce the need

for future surgeries due to compromised surgical margins (a characteristic of this type of melanoma).

The number needed to excise (NNE) corresponds to a ratio between the number of benign lesions excised and the number of melanomas histologically diagnosed in the same period of time. It defines and represents an indicator of performance in melanoma detection and proved RCM can reduce the NNE improving diagnostic accuracy, [56,57,58] improving also the specificity for the diagnosis of melanoma when associated with dermoscopy, as a second-level evaluation, for suspicious lesions. [43]

NNE can also be used as a tool for an estimative of cost-effectiveness, since the highest cost for the diagnosis of melanoma is due to biopsies / excisions, preparation of the material for analysis and histological evaluation. In 2016, Pellacani et al demonstrated that the NNE after the use of the RCM was 6.25 while the NNE only with dermoscopy was 19.41, demonstrating that the RCM can reduce in 2/3 the number of benign lesions excised. In this same study, the group concluded that the use of the RCM could lead to a saving of 260,000 Euros for each 1 million inhabitants examined, which corresponded to a reduction of 30% of the total value spent when this technology was applied. In addition, it was estimated a 43% reduction in waiting time for surgeries. [59]

With RCM it is possible to distinguish melanocytic malignant proliferation in different types of melanoma, thus enabling an easier differential diagnosis towards both melanocytic and non-melanocytic benign lesions. Regarding the most common melanoma type, the superficial spreading melanoma (SSM) we can distinguish two different morphological patterns: pagetoid melanoma and solar melanoma.

In RCM the pagetoid subtype shows irregular honeycombed or cobblestone pattern (depending on the intensity of pigmentation). In cases of abundant pagetoid spread, epidermis can display important disarray. Pagetoid spread in this type of melanoma is characterized by

large nucleated cells (>20μm, twice the size of keratinocytes) [60] that may be classified, according to the distribution, into localized (cells detected in a small área of the lesion) or widespread. In the dermo-epidermal junction (DEJ) atypical meshwork is the predomint pattern, due to the presence of junctional melanocytic aggregates widening and distorting the rete-ridges, [61] and atypical roundish cells can be visualized. In the upper dermis of the pagetoid SSM nests can be seen, mostly of them being classified as “dense and sparse” - “dense and sparse nests” display individual pleomorphic roundish cells loosely packed.[62] On the other hand, the solar melanoma (the other SSM subtype) is represented by atypical dendritic melanocytes in both epidermal and DEJ levels which can be very numerous resembling a carpet of bright branching structures. In the epidermis of this type of melanoma we find atypical or disarranged honeycomb or cobblestone pattern and epidermotropism of atypical cells in diverse morphologies (pleomorphic cells) with branches which can appear as thick and short dendrites or thin bright filamentous. This dendritic cell proliferation reminds the one found in LM, with a difference that in the later they are preferentially located around hair folicles (folliculotropism). [63,64] In the DEJ ringed or meshwork pattern is usually observed along with single atypical cells. When these cells form aggregates they are organized in juctional clusters sheets of cells where the body of these cells are not easily identified but their dendrites are strongly close to each other. The effacement of the DEJ and the thinning of the epidermis lead to a progressive disappearing of the ringed pattern, the papillary contour is not visible anymore and the pattern of the DEJ architecture becomes aspecific/undefined. In the upper dermis we notice marked solar elastosis displaying coarse and huddle collagen bundles.[65]

From the moment melanoma becomes invasive, cells become pleomorphic in size and shape, and both round and dendritic cells are present, with tendency to form clusters, large aggregates and sheets of cells infiltrating the dermis. Cerebriform nests composed by

hyporrefrective aggregates of small cells outlined by bright collagen septae that are suggestive of deep dermal invasion are frequently present at this stage. [66]

In pure nodular melanoma, where intra-epidermal proliferation is usually absent or very limited, pagetoid cells are absent. [67] However, pleomorphic atypical melanocytes are frequently distributed in sheet-like structures, and in nests in the superficial dermis. In this type of melanoma, cerebriform nests are more frequently seen and they are correlated to deep infiltration of the tumor.

Optical coherence tomography is a noninvasive imaging technique that provides vertical and horizontal images of the skin and reaches a depth of up to 1.5mm.[68] Unlike RCM the resolution of the images is not good enough to distinguish cells, therefore evaluations with OCT are based on changes in the general architecture of the lesion. For this reason, in dermatology it is well applied in the diagnosis of epithelial skin cancers but is not appropriate for diagnosing melanoma. [69,70,71,72]

In 1991, before the application in dermatology, it was demonstrated that OCT was able to image the retina, vitreous, optical disc of the human eye, and the human coronary artery. In the occasion histologic correlations of the same areas were done.[73] After that, OCT technique has been fully applied in Ophtalmology, for example in the measurement of human retinal structure and evaluation about macular disease, [74,75] and other medical fields as Urology, [76,77] and Gastroenterology. [78]

Regarding the use of OCT for the diagnosis of nonmelanoma skin cancer it has been established its importance in the diagnosis of basal cell carcinoma (BCC) including the classification into subtypes, [79,80] the definition of the margins of BCC before micrographic surgery, [81] and to distinguish between BCC, actinic keratosis, Bowen disease and squamous cell carcinoma. [72,82]

The first description about the application of OCT in dermatology dates from 1997. In that occasion it was stated that OCT could be a promising new imaging method for visualization of morphologic changes of superficial layers of human skin. OCT was suggested to be a useful noninvasive diagnostic tool not only in the field of skin cancer but also in bullous diseases, [83] and inflammatory skin diseases, for example. [84]

In the history of OCT applied in dermatology, 3 devices have been developed: a swept-source multi beam frequency domain OCT, a spectral domain-OCT (SD-OCT) and a time domain high-definition-OCT (HD-OCT), each one with different characteristics. The frequency domain OCT device VivoSight® (Michelson Diagnostics, Kent, UK) offers a lateral resolution < 7.5 μm with an axial resolution of 10 μm and a penetration depth ranging from 1.5 to 2 mm. Because of the possibility to use the multi-slice function, VivoSight®, based on the technique of Michelson interferometry, reaches a three-dimensional scanning of around 6 mm x 6 mm x 2 mm. The light source corresponds to a laser at a wavelength of 1305 nm.[c]

The SD-OCT system Callisto® (Thorlabs AG, Lübeck, Germany) offers a lateral resolution of about 8 μm with a lateral scan length of up to 10 mm, an axial resolution < 7 μm and a penetration depth of 1.7 mm, providing only cross-sectional images. It uses a 930 nm super luminescent diode as the light source, with a broadband and lower coherence light.[d]

The HD-OCT Skintell® (AGFA, HealthCare, Mortsel, Belgium) offers high axial and lateral resolution of 3 μm and reaches a penetration depth of about 750 μm. It is able to take 2D images with a field of view of 1.8 mm x 1.5 mm, with a possibility to catch cross-sectional (slices) and horizontal (en face) images in real time building 3D images. This OCT system works with a a near infrared range at about 1000 – 1700 nm, and an application of an optical matching gel between the glass plate of the hand piece and the skin surface is

[c] Michelson Diagnostics. VivoSight OCT Scanner- Technical Specification. Available from: http://www.vivosight.com/wp-content/uploads/2013/02/1003.SP_.638-Issue-1-VivoSight-Technical-Specification.pdf.

[d] Thorlabs Gmbh. Callisto Spectral Domain OCT System: Operating Manual, 2011. Available from: https://www.thorlabs.com/thorcat/21200/CALLISTO-Manual.pdf.

necessary for image acquirements.[e]

A comparison among these 3 OCT systems showed all can significantly distinguish BCCs and actinic keratosis from adjacent healthy skin. It was noted that Vivosight® and Callisto® correlated well regarding tumor thickness, unlike Skintell® (which had much lower detection depth). This difference was correlated to differences on light source, focus and lens system. [85]

In 2015 during an European Union Project, Vivosight®, an OCT producer, developed a software able to detect the blood flow in skin lesions during real time.[86] The equipment is called Dynamic-OCT (D-OCT) and many studies could prove the in vivo vascular changes according to the type of skin lesions.

[e] AGFA HealthCare. Skintell Datasheet. Available from: http://www.agfahealthcare.com/global/en/he/library/libraryopen?ID=34-711786

2. OBJECTIVES:

In a scenario of emerging technologies, which are promising for early and accurate melanoma diagnosis and for melanoma characterization, increase in melanoma incidence, and attention to cancer prevention and early diagnosis, also due to the increasing therapeutic costs generated by the introduction of novel biotechnological molecules, we focused our attention to:

- **study the application and validity of advanced non-invasive methods to obtain clinical information useful for the clinical management of the patient with melanoma.**
- **evaluate the applicability and validity of noninvasive methods to obtain useful information for the clinical management of patients with cutaneous melanoma.**
- **evaluate, from an economic perspective, confocal microscopy compared to dermoscopy, for the diagnosis and clinical management of patients with cutaneous melanoma in order to reduce the costs of treating this disease in Brazil.**
- **discuss the transversalities between the model of care for cutaneous melanoma patients in Italy and Brazil, from the economic perspective.**

3. STUDIES CONDUCTED DURING PHD ON APPLICATION OF ADVANCED TECHNOLOGIES FOR MELANOMA CHARACTERIZATION:

To reach the main objectives, tumor characteristics were evaluated by RCM and OCT (the two mostly advanced technologies available in dermatology) in order to identify new morphological patterns characteristic for the different types of melanoma. Through these studies, it was possible to validate the capability of each of these instruments to provide information useful for patient management.

In parallel, we explored OCT vascular morphology, dedicating to determine and validate patterns and features, and to evaluate their correlation with melanoma aggressiveness, and RCM feature significance in the contest of difficult to diagnose lesions. As identified the most relevant diagnostic feautures in RCM for different types of melanoma, we focused on the development of simplified algorithm in order to facilitate the learning process and to enhance its ready-to-use application. Finally, analysing the situation in Italy, and in particular in the diagnostic setting implemented in Modena Province, we estimated through cost analysis studies the transferability of the Modena workflow into the Brazilian system.

OPTICAL COHERENCE TOMOGRAPHY STUDIES:

I. VASCULAR MORPHOLOGY DEFINITION:

During the time of my PhD project I participated in an European Union Project (ADVANCE, Automatic Detection of VAscular Networks for Cancer Evaluation, Grant No. 621015) for the evaluations of benefits and usefulness of the inserption of a software able to

analyse in vivo vascularity of skin lesions, named Speckle Variance Optical Coherence Tomography and later Dynamic Optical Coherence Tomography (D-OCT).

This novel variant of OCT, corresponding to a microangiography of the skin, showed the abbility to visualize and measure the vascular morphology. Vascular imaging is usually limited to <500 μm because of the speckle noise/signal ratio in the deeper parts of the skin. The dynamic OCT data are collected simultaneously with the structural OCT data and are immediately displayed on the structural OCT images as an overlay, so that the relationship between the vessels and structures can be seen. Images are displayed in enface and transversal sections and areas of blood flow are displayed as red.

Ulrich M, Themstrup L, De Carvalho N, Ciardo S, Holmes J, Whitehead R, Welzel J, Jemec GBE, Pellacani G. Dynamic optical coherence tomography of skin blood vessels - proposed terminology and practical guidelines. J Eur Acad Dermatol Venereol. 2018;32:152-155. [87]

Due to the possibility to distinguish different vascular shapes and to analyse their distribution and organization within skin lesions a proposed terminology and practical guidelines were described and it was standardized they should be classified through enface sections.

According to the morphology vessels were classified as dots (small red points corresponding to vessels oriented vertical to the surface), blobs (larger round to oval red globules corresponding to vessels oriented vertical to the surface), coiled vessels (spiral-like or convoluted lines/circles), linear (fine lines), curved (comma-like lines) and serpiginous vessels.

The distibution of vessels could even be classified as regular (the same pattern present thoughout the whole image), clustered (presence of areas with a group of vessels with the

same pattern) or irregular (chaotic distribution and different aspects os vessels in the same image). Moreover dots, blobs and coiled vessels could be described as “mottled” (when distributed in limited but sharply demarcation), whereas linear vessels could be defined as a “mesh” when they were interconnected generating a reticular structure.

For linear, curved and serpiginous vessels the presence of branches could also be evaluated and classified as “arborizing” (with a progressive decrease in the thickness of the subsequent branches) or “bulging” (if enlarged buds/dilations originated from the main structure).

Schuh S, Holmes J, Ulrich M, Themstrup L, Jemec GBE, De Carvalho N, Pellacani G, Welzel J. Imaging Blood Vessel Morphology in Skin: Dynamic Optical Coherence Tomography as a Novel Potential Diagnostic Tool in Dermatology. Dermatol Ther (Heidelb). 2017;7:187-202. [88]

Subsequent evaluation of healthy, inflammatory and neoplastic skin lesions were used to test vascular parameters in variable conditions, and showed different vascular characteristics, therefore suggesting D-OCT as a potential diagnostic tool in dermatology.

Themstrup L, De Carvalho N, Nielsen SM, Olsen J, Ciardo S, Schuh S, Nørnberg BM, Welzel J, Ulrich M, Pellacani G, Jemec GBE. In vivo differentiation of common basal cell carcinoma subtypes by microvascular and structural imaging using dynamic optical coherence tomography. Exp Dermatol. 2018;27:156-165. [89]

Regarding basal cell carcinoma, it has been also demonstrated how D-OCT may help in the definition of the subtype according to the vascular aspects predominantly found in each BCC subtype. Not only the possibility to predict BCC subtype at bedside of the patient before excision may help in the choice of adequate therapy according to the subtype of the tumor,

but also defines the variability of vascular pattern in the contest of the same tumor according with tumor subtype, pattern of growth and tumor burden.

II. VASCULAR STUDIES IN MELANOMA PROGRESSION:

De Carvalho N, Ciardo S, Cesinaro AM, Jemec G, Ulrich M, Welzel J, Holmes J, Pellacani G. In vivo micro-angiography by means of speckle-variance optical coherence tomography (SV-OCT) is able to detect microscopic vascular changes in naevus to melanoma transition. J Eur Acad Dermatol Venereol. 2016;30:e67-e68. [90]

Vascular parameters are relevant for tumor growth. In melanoma they are related with tumor aggressiveness. We proceeded to study the in vivo vascular pattern in order to identify its dynamics during tumor progression. First a case report showed important changes in the microvascular organization in the transition from nevus to in situ melanoma, in a melanoma arising on a nevus. In the area corresponding to the benign junctional proliferation, D-OCT displayed regular distribution of dotted vessels assuming a regular reticulated architecture in the enface view - the pattern did not differ so much from the vascular pattern of the healthy surrounding skin. On the other hand, in correspondance to the in situ melanoma, densely packed dotted vessels were observed in the enface view. The description suggested these micro-angiographic changes may help to identify early events occuring in the malignant march.

<u>De Carvalho N</u>, Welzel J, Schuh S, Themstrup L, Ulrich M, Jemec GBE, Holmes J, Kaleci S, Chester J, Bigi L, Ciardo S, Pellacani G. The vascular morphology of melanoma is related to Breslow index: An in vivo study with dynamic optical coherence tomography. Exp Dermatol. 2018;27:1280-1286. [91]

After the observation of these microvascular changes from nevus to in situ melanoma, being neoangiogenesis (the growth of new vessels) crucial for tumor progression and growth, which is associated to metastasis and poor prognosis, we thought to evaluate whether these microvascular changes could vary in accordance to Breslow thickness, which represents the strongest predictor of tumor aggressiveness.

In the present study, a retrospective D-OCT blind evaluation of 127 melanomas was carried out. In the occasion, the enface view of the cases was evaluated taking into account the vascular patterns, distribution of vessels and presence of branches following the already described features and patterns. Enface images were evaluated at 3 different depths: 150, 300 and 500 μm. For statistics analysis and correlation between vascular morphologies and Breslow thickness, lesions were grouped into 5 subgroups according to melanoma Breslow thickness: group 0 (in situ), group I (≤1mm), group II (>1, ≤2mm), group III (>2, ≤4mm) and group IV (>4,0mm).

According to the improvement in thickness, a polymorphism of vessels was identified at 150 and 300 μm. At 150 μm, regular distribution of dotted vessels was more prevalent in groups 0 and I, whereas an irregular distribution of this vascular morphology was predominant in melanomas thicker than 1mm ($P = 0.031$), serpiginous vessels with bulging branches were predominantly seen in melanomas thicker than 2 mm ($P < 0.001$). At the depth of 300 μm, irregular distribution of dotted vessels was also predominant in lesions thicker than 1mm ($P = 0.021$) and serpiginous vesseles with bulging branches in lesions thicker than

2 mm ($P < 0.001$). At the depth of 500 μm the background noise hampered vessel detection making impossible the correlation.

According to this data, vascular aspects in D-OCT were in accordance to Breslow thickness. Thus, authors concluded in vivo vascular study could be linked to tumor aggressiveness and possible capability of melanoma metastatization.

REFLECTANCE CONFOCAL MICROSCOPY STUDIES:

I. DEFINITION OF MORPHOLOGICAL AND CHARACTERISTICS ASPECTS IN DIFFICULT TO DIAGNOSE LESIONS:

A. MELANOMAS ON THE FACE:

Lentigo maligna, a melanoma on sun-damaged skin, is mostly found in head and neck of elderly patients. In the very early phase it overlaps dermoscopic features with other benign flat pigmented lesions in the face, hampering the right diagnosis.

In situations when clinical and dermoscopic images are equivocal, when lesions are poorly defined or when differential diagnosis with benign lesions is difficult, RCM evaluation can be extremely helpful. Nevertheless, LM can be in collision to other benign lesion in the face – also in these cases RCM shows to be very helpful in diagnosing LM correctly.

Chen LL, Scope A, De Carvalho N, Rabinovitz HS, Pellacani G. Difficult-to-diagnose facial melanomas: Utility of reflectance confocal microscopy in uncovering the diagnosis. JAAD Case Rep. 2017;3:379-383. [92]

A retrospective RCM evaluation of 4 dermoscopically difficult-to-diagnose but histologically proven LM (1 small macule, 1 small papule, 1 melanoma mimicking a keratinocytic neoplasm upon dermoscopy and 1 melanoma mimicking solar lentigo) proved RCM features were present for LM diagnosis by the presence of abundant atypical melanocytic proliferation, pagetoid spread, and cellular pleomorphism. Thus, it confirmed that RCM in combination with dermoscopy increases the diagnostic accuracy for melanoma.

However, the presence of bright fillaments/dendritic cells around hair follicles have been also described in the epidermal layer of RCM in PAK, [93] making challenging the differential diagnosis between this entity and LM.

Persechino F, De Carvalho N, Ciardo S, De Pace B, Casari A, Chester J, Kaleci S, Stanganelli I, Longo C, Farnetani F, Pellacani G. Folliculotropism in pigmented facial macules: Differential diagnosis with reflectance confocal microscopy. Exp Dermatol. 2018;27:227-232.[51]

This motivated us to study the differences regarding the dendritic cells in PAK and LM. In the occasion, 154 pigmented facial macules (76 LM/LMM and 78 non-melanocytic skin neoplasms, 28 of them corresponding to PAK) were retrospectively evaluated with RCM according to the already-described RCM parameters. In addition, we focused on the description of new RCM parameters depicting aspects of the follicle and presence of bright dendrites. In conclusion, in malignant melanocytic lesions it has been described a follicular infiltration of bright dendrites in 68.4% of the cases, whereas in PAK only in 7.1% of the time it has been detected. In the present study we identified the presence of follicular infiltration of

bright dendrites as a very sensitive and specific parameter to be used for the early identification and differential diagnosis of LM.

It is known that it is difficult to treat LM because of the special location where it usually appears (face) and also because of the characteristic recurrence.

Pellacani G, De Carvalho N, Ciardo S, Ferrari B, Cesinaro AM, Farnetani F, Bassoli S, Guitera P, Star P, Rawson R, Rossi E, Magnoni C, Gualdi G, Longo C, Scope A. The smart approach: feasibility of lentigo maligna superficial margin assessment with hand-held reflectance confocal microscopy technology. J Eur Acad Dermatol Venereol. 2018;32:1687-1694.[53]

Aiming to help the definition of the margin within a cellular level and avoiding both, too much healthy skin resection and necessity of multiple surgeries because of histologic positive margin, we sought to evaluate the feasibility of RCM for the definition of the lateral margins of LM.

Twenty-three cases with biopsy-proven LM or clear-cut melanoma features on wide-probe-RCM were recruited. Firstly, clinical and dermoscopic determination of visible margins were made with dermsocopy (Score I). Keeping a distance of 2 mm far from the outer border, a dermographic pen was used to draw the first score parameter to be evaluated. The margin of the lesion was then anesthesized either by subcutaneous infiltration or occlusive application of topical anaethetic 1 hour prior. A superficial cut was then made with either a scalpel or a tip of a needle, overlying the dermographic pen line at 4 or more cardinal points. Next step was the position of the hand-held probe of RCM in the center of the lesion manoeuvering it outwards in a linear direction until Score I was visualized. Once Score I was identified, the area beyond the cut was examined for features of melanoma. RCM margin was considered negative when specific findings were absent in at least 2 fields-of-view (>1.7mm) inward

from the cut and completely absent outward from the cut. If margin was positive but did not extend beyond Score I, the RCM probe would be removed and a further cut would be made 2 mm away from Score I, becoming this Score II. However, if the positive margin extended outward beyond Score I, the exact number of positive-melanoma RCM fields-of-view were counted and a radial distance of 2 mm from the outermost positive RCM field was made, becoming Score II. This step continued until all RCM margins were negative. After that, patients followed to surgical excision of the lesions. If lesion was located close to an important facial structure (e.g. eyes) excision followed exactly the RCM demarcation. Differently for LM not close to important facial structures an additional safety margin of 3 mm was attained beyond RCM-defined margins. All patients were followed by dermoscopic and RCM evaluation after 6 and 12 months with no recurrence feature so far.

This technique named SMART appeared to be feasible for margin mapping of melanomas on the face.

B. MELANOMAS ON THE BODY:

Pigment network is an important dermoscopic feature for melanocytic lesions. A detailed evaluation of its characteristics is important for differential diagnosis between benign and malignant melanocytic lesions, once melanomas usually present with a thicker pigment network.

De Pace B, Farnetani F, Losi A, Ciardo S, <u>De Carvalho N</u>, Cesinaro AM, Reggiani Bonetti L, Chester J, Kaleci S, Del Duca E, Nisticò SP, Longo C, Pellacani G. Reinterpreting dermoscopic pigment network with reflectance confocal microscopy for identification of melanoma-specific features. J Eur Acad Dermatol Venereol. 2018;32:947-955. [94]

In order to identify RCM features in correspondance with thin, thick and mixed pigment network for differential diagnosis between benign and malignant melanocytic lesions (nevi and melanoma, retrospectivelly), a retrospective RCM evaluation of a huge number of melanocytic lesions located on the trunk and limbs was made. All lesions were histologically confirmed and, to be included in the study, they should be dermoscopically characterized mainly by pigment network (more than 90% of the lesions surface).

Thin network was represented by delicate, thin and less pigmented lines; thick network was represented by heavy lines with high density. When both of these features were present in the context of the same lesion, network was classified as mixed.

Thin network in melanoma was characterized by honeycomb pattern ($P < 0.001$), dendritic cells ($P < 0.001$), atypical ringed pattern ($P = 0.035$) and stuctureless area ($P = 0.012$). In the thick network of melanomas, RCM features in correspondence were round cells ($P < 0.001$), dendritic cells ($P < 0.001$), and atypical meshwork pattern ($P < 0.001$). Melanomas with mixed pigment network shared honeycombed ($P = 0.049$), and typical ringed patterns ($P = 0.045$) in the thin area whereas round cells ($P < 0.001$) and atypical meshwork pattern ($P < 0.001$) were present in the thick area.

In conclusion, we demonstrated that RCM can improve the diagnostic accuracy for the differential diagnosis between melanocytic lesion (nevi and melanoma) presenting mainly pigment netwok pattern in dermoscopy.

It has been already described melanomas have different clinical presentation and biological behavior as, for example, nodular melanoma grows rapidly whereas lentigo maligna tends to grow slowly. Histopathologic examination can identify melanoma features linked with dynamic and slow progression. [95] Therefore it is important to recognize features especially for the early stages, which enables qualification for the treatment of patients. [44]

Kardynal A, Olszewska M, de Carvalho N, Walecka I, Pellacani G, Rudnicka L. Reflectance confocal microscopy features of thin versus thick melanomas. G Ital Dermatol Venereol. 2019;154:379-385. [96]

In the present study our aim was to assess typical RCM features of thin (≤1 mm according to Breslow thickness) and thick (>1 mm) melanomas.

Thirty lesions comprising 50% thin and 50% thick melanomas were retrospectivelly evaluated in RCM. As results we found edged papillae (P = 0.032) and honeycombed or cobblestone pattern (P = 0.068) more frequently observed in thin melanomas, both features being also present in benign melanocytic lesions, therefore being good prognostic factors. Differently in thick melanomas roundish cells (P = 0.001), non-edged papillae (P = 0.006), numerous pagetoid cells (P = 0.028), numerous atypical cells at dermal-epidermal junction (P = 0.058) and epidermal disarray (P = 0.068) were more frequently observed.

Based on our results we hypothesized a progression model of melanoma to be considered in further studies not only to predict tumor thickness but also to understand biomolecular changes during tumoral invasion.

II. TOOLS / ALGORITHMS FOR DIFFERENTIAL DIAGNOSIS AND TRANSFERABILITY TO NON-EXPERTS:

A. CHALLENGING LESIONS: APPLICATION OF REFLECTANCE CONFOCAL MICROSCOPY IN LESIONS MIMICKING MELANOMA:

Basal cell carcinoma is the most frequent type of skin cancer. Dermoscopic features of typical BCC have been widely described, but in some cases this neoplam may share clinical and dermsocopic features with other skin conditions, tumoral and inflammatory. It makes the adequade diagnosis very challenging as they may present blue-white veil, multiple brown dots, pseudopods, atypical pigment network or radial streaks – dermoscopic features usually associated with melanoma. So far, few short reports or case series have reported dermoscopic atypical BCC.

Peccerillo F, Mandel VD, Di Tullio F, Ciardo S, Chester J, Kaleci S, de Carvalho N, Del Duca E, Giannetti L, Mazzoni L, Nisticò SP, Stanganelli I, Pellacani G, Farnetani F. Lesions Mimicking Melanoma at Dermoscopy Confirmed Basal Cell Carcinoma: Evaluation with Reflectance Confocal Microscopy. Dermatology. 2019;235:35-44. [97]

As RCM enables in vivo imaging at nearly histological resolution we sought to evaluate with RCM dermoscopic atypical melanocytic lesions according to common RCM criteria for the differential diagnosis of BCC and to identify parameters indicative for the classification of BCC into superficial (sBCC) or nonsuperficial (nsBCC) subtypes.

A total of 178 atypical lesions that were firstly diagnosed as melanomas according to dermoscopy were retrospectivelly evatuated with RCM. Thirty-four of those were later

diagnosed as BCC through RCM, followed by histologic confirmation. It proved RCM is able to correct diagnose BCC even in atypical cases.

We also aimed to identify the possibility to classify BCC according to RCM features. It would be important for the right therapeutic chosen, once sBCC has low recurrence rate and can be non-surgically treated, differentely from nsBCC. In the present study we found RCM was able to adequately classify the subtype of BCC in over 90% of the cases. The presence of cords connected to the epidermis, absent vascular morphology and solar elastosis were parameters positive for sBCC, whereas large tumor islands with branch-like structures located in the dermis, peripheral palisading, peritumoral clefts, coiled vascular morphology and increased vascular diameter, collagen surrounding the tumor island and the abscence of cords connected to the epidermis were RCM features associated with nsBCC.

Seborrheic keratosis (SebK) is one of the most common benign skin tumors, usually dermoscopic evaluation is enough for an adequate diagnosis and this skin condition represents no risk for patient. However, clinically and dermoscopically unusual cases are increasingly reported. These specific lesions sometimes mimic melanoma and their final excision is often required in order to reach a correct diagnosis. To complicate even more the scenario, melanomas mimicking SebK have been also reported. [98]

Pezzini C, Mandel VD, Persechino F, Ciardo S, Kaleci S, Chester J, De Carvalho N, Persechino S, Pellacani G, Farnetani F. Seborrheic keratoses mimicking melanoma unveiled by in vivo reflectance confocal microscopy. Skin Res Technol. 2018;24:285-293. [99]

Taking into account how challenging can be the right diagnosis of a SebK and also knowing some melanomas can dermoscopically mimic SebK the aim of this study was to

evaluate the reliability of well-known RCM criteria for SebK identification in a group of lesions with atypical dermoscopy presentation, mimicking melanoma.

The study consisted of a retrospective RCM evaluation of a total of 117 lesions with clinical diagnosis of atypical melanocytic lesions, and all lesions were excised for histologic confirmation. After RCM analysis, 71 of these cases were classified as SebK, with a histologic agreement of 97%.

We could conclude RCM proved a high agreement with histolpathology for SebK with atypical dermoscopy presentations allowing an early differential diagnosis, which may assist clinician therapeutic decision and avoid unnecessary excisions.

B. CONFOCAL ACCURACY IN NON-EXPERT AND TECHNOLOGY TRANSFERABILITY:

RCM is a newly adopted technology and limitation to proper and diffusion may be due to the limited number of expert users in the field and lack of dedicated training programs to properly support the necessary knowledge acquisition and experience needed for safe and effective implementation in clinical practice.

With the potential for an increase in requests for distant expert consultation of RCM images there is a need to provide proper, accurate and safe management of lesions sent for second expert consultation and in addition provide an available and effective training program for new users.

Witkowski AM, Łudzik J, Arginelli F, Bassoli S, Benati E, Casari A, De Carvalho N, De Pace B, Farnetani F, Losi A, Manfredini M, Reggiani C, Malvehy J, Pellacani G. Improving diagnostic sensitivity of combined dermoscopy and reflectance confocal microscopy imaging through double reader concordance evaluation in telemedicine settings: A retrospective study of 1000 equivocal cases. PLoS One. 2017;12:e0187748. [40]

According to the previous statement, our objective was to improve diagnostic sensitivity of RCM image diagnosis using a double reader concordance evaluation approach and to reduce mismanagement of equivocal cutaneous lesions in retrospective consultation and telemedicne settings.

A thousand combined dermoscopy-RCM image sets were evaluated in blind by 10 readers with advanced training and internship in dermsocopy and RCM evaluation. There was made a comparison between the sensitivity and specificity of single readers evaluation versus double reader concordance evaluation, as well as the effect of diagnostic confidence on lesion management in a retrospective setting.

Our results showed that single reader evaluation resulted in an overall sensitivity of 95.2% and specificity of 76.3%, with misdiagnosis of 8 melanomas, 4 BCC and 2 squamous cell carcinomas. Combined double reader evaluation resulted in an overall sensitivity of 98.3% and specificity of 65.5%, with misdiagnosis of 1 in situ melanoma and 2 BCC.

In conclusion, double reader blind concordance evaluation may improve the sensitivity of diagnosis and management safety. The use of a second check can be implemented in telemedicine settings where expert consultation and second opinions may be required.

Pellacani G, Scope A, Gonzalez S, Guitera P, Farnetani F, Malvehy J, Witkowski A, De Carvalho N, Lupi O, Longo C. Reflectance confocal microscopy made easy: The 4 must-know key features for the diagnosis of melanoma and nonmelanoma skin cancers. J Am Acad Dermatol. 2019;81:520-526. [100]

RCM diagnostic expertise needs a long time of tranining and dedication, accumulation of personal experience and exposure to rare cases. Besides, there are only few basic courses on RCM worldwide and the timing is not enough for new users to learn and apply the technique confidently. Due to this, the present study aimed to identify a short list of key RCM features for skin cancer diagnosis and test their diagnostic utility.

Six RCM experts using a modified Delphi method identified 4 RCM key features (atypical cells, DEJ disarray, basaloid cords/islands, and keratinocyte disarray). To test their diagnostic utility 10 beginner RCM readers evaluated a subset of 100 RCM cases of benign and malignant skin neoplams.

RCM experts identified 18 RCM features as highly valuable for skin cancer diagnosis. On the basis of consensus definitions, these RCM features were further clustered into 2 melanoma-specific key features (atypical cells and dermoepidermal junction disarray), 1 basal cell carcinoma specific key feature (basaloid cords/islands), and 1 squamous cell carcinoma specific key feature (keratinocyte disarray). The novice reading study showed that the presence of at least 1 of the 4 key features was associated with an overall sensitivity for skin cancer diagnosis of 91%, with sensitivity for melanoma of 93%, sensitivity for basal cell carcinoma of 92%, and sensitivity for squamous cell carcinoma of 67%, and an overall specificity of 57%.

In conclusion, the simplified approach presented herein may enhance novice RCM readers's accuracy for skin cancer diagnosis and facilitate the diffusion of RCM to dermatology clinics beyond academic centers.

Considering this thesis was developed based on a co-tutela between the University of Modena and Reggio Emilia and the Universidade Federal do Estado do Rio de Janeiro (UNIRIO), with the purpose to better identify the differences and transversalities in the models about skin cancer screening and its repercussions in the amount of melanomas diagnosed in early or advanced stages, we opted for a brief presentation for each of them:

4. COST-EFFECTIVENESS STUDY (COMPARING ITALIAN - MODENA - AND BRAZILIAN SYSTEMS)

A. MODENA SYSTEM:

The Department of Dermatology of the University of Modena and Reggio Emilia (UNIMORE), Italy, proved how much the Italian Health System has benefited with the improvement on skin cancer diagnosis. It was due to an improvement of skills and knowledge in dermoscopy combined with the introduction of RCM in dermatologic daily routine, as second-level-evaluation in doubtful cases. Benefits are not limited to cost and savings [59] but also regarding personal health quality and life expectancy, once diagnoses are done earlier. For this reason, a brief history of the "Modena model system" will be made in order to make easier the comparison between it and the "Brazilian model system", and the possible benefits of the introduction of RCM in the country.

Untill the year 2011 the diagnosis of skin cancer was made based on the history of the lesions followed by body check with dermoscopic examination of each lesion (Modena model 1). Based on the documentation of histological results of melanomas excised in the years 2009, 2010 and 2011 in the Dermatology department of UNIMORE, it was calculated that **28.8%** corresponded to stage 0 [in situ melanoma (MIS)], **46.6%** was diagnosed at stage I, **10.6%** at stage II, **7.5%** at stage III and **6.3%** at stage IV. In order to make easier the

understanding of the percentages, and considering the stages that present more risk to develop metastasis based on the TNM classification according to the 8th Edition of the American Joint Committee on Cancer,[101] data was classified into 3 groups: MIS, thin (stages I and II) and thick melanomas (stages III and IV). In this way, **28.8%** were diagnosed as MIS, **57.3%** as thin and **13.9%** as thick melanomas.

In February 2012, RCM was introduced in the Dermatology department of UNIMORE for systematic clinical use (being applied for research since 2003), and started to be used in dermatological routine during skin cancer screening for difficult lesions complementary to dermoscopy (Modena model 2). Along with RCM introduction in the diagnostic workflow, a systematic reorganization of the service has been implemented, with direct access for patients presenting a suspicious lesion, after check of General Practitioner (GP) as per standard in the Italian Health System. Moreover, GPs have been not only informed of the facilitated access for suspicious lesions, but instruction and formation on the basic rules to recognize and to do not miss a skin cancer were provided in the mandatory continuing medical education programs for GPs. Following the same classification as adopted for Modena model 1, the documentation of histological results of melanomas diagnosed in the Dermatology department of UNIMORE during the years 2012, 2013, 2014, 2015, 2016, 2017 and 2018 was calculated according to clinical stages: **40.3%** corresponded to stage 0, **44.4%** to stage I, **7.8%** to stage II, **4.3%** to stage III and **3.2%** to stage IV. Grouping them as MIS, thin and thick melanomas (as done for Modena model 1), we have for Modena model 2 the following: **40.3%** diagnosed as MIS, **52.2%** as thin and **7.5%** as thick melanoma.

In 2014, Pellacani et al proposed a study to measure the potential impact of reflectance confocal microscopy to implement melanoma diagnosis following the workflow. In the study, atypical melanocytic lesions were referred for either RCM documentation (when clinical/dermoscopic criteria were in accordance to melanoma and excision would be

proceeded anyway) or RCM consultation (when doubtful/equivocal lesions were evaluated by RCM and their definite outcome were dictated by RCM findings). Results showed RCM influenced the outcome in two-thirds of the lesions, saved over 50% of benign lesions from uneccessary excision, and NNE was 6.8 with RCM evaluation compared with hypothetical 14.6 without RCM evaluation. The group demonstrated that the systematic use of RCM can reduce the number of benign lesions excised and minimize the risk of referring a melanoma to dermocopy monitoring and potencially losing the patient to follow-up. [42]

A meta-analysis recently published by Xiong et al explains the success of Modena Model 2 after the incorporation of RCM into daily practice during skin cancer screening, as a complementary examination in cases of difficult / doubtful lesions first evaluated with dermoscopy. The comparison between the percentages of melanoma classified into stages in Modena Model 1 and Modena Model 2 shows an improvement in diagnostic accuracy in the last one.

At this meta-analysis Xiong et al compared the diagnostic accuracy of dermoscopy and RCM for the diagnosis of malignant skin tumors. A systematic eletronic literature search was conducted including PubMed, Medline, Embase, Cochrane Library database and Web of Science up to April 26, 2016. Eight published studies were included in the analysis, and Pooled aditional detection rate, diagnositic accuracy and 95% confidence intervals were calculated using STATA and Meta-Disc analysis. RCM showed to increase significantly the detection rate of malignant skin tumors by 7.7% (95% CI 0.01-0.14). The specificity of dermoscopy was significantly lower than that of RCM [52.9% (95% CI 0.49-0.57) and 80.3% (95% CI 0.77-0.83), respectively]. The pooled sensitivity and specificity of RCM for melanoma detection were also higher than those of dermoscopy, with more disparity regarding the pooled specificity [78.8% (95% CI 0.75-0.82) for RCM and 49.1% (95% CI 0.45-0.53) for dermoscopy]. According to the differences obtained in the results, the authors

concluded RCM has significantly higher diagnostic specificity for malignant skin tumors, and so could improve their detection rate. [102]

Moreover, on the year 2016 Pellacani et al showed how RCM can directly affect the costs of the Italian Health System. Assuming that a suboptimal diagnostic accuracy leads to excision of a high number of benign lesions with consequent costs, an improvement on the diagnostic specificity would reduce unnecessary excisions, which would reflect on the reduction of costs. Cost-analysis was performed under the Hospital point of view (UNIMORE) for each procedure (dermatologic outpatient exam, digital demoscopy, follow-up visit, complete narrow-margin surgical excision, histopathologic exam, medication/suture removal). The authors showed that avoiding unnecessary excisions, an overall yearly saving of over 260.000 Euros can be expected for every million inhabitants evaluated with RCM. This study retrospectivelly evaluated the impact of RCM implementation in a real clinical scenario and also concluded that to reduce the increasing burden of costs for cancers in the Health System, prevention and early detection are necessary since costs dramatically increase with melanoma stage. [59]

B. BRAZILIAN SYSTEM:

Brazil has more than 200 million inhabitants and counts with a public health system called Sistema Único de Saúde (SUS) as the main health provider which, in terms of law, is obliged to provide all healthcare assistance for the citizens at no cost. More than 75% of the brazilian population have access only to this public healthcare assistance which is very limited regarding the access to dermatologists. The other 25% of the population is assisted by health insurance or private doctors.

Currently in Brazil dermoscopy is the main instrument used for the evaluation of skin lesions suspicious for malignancy. Unfortunately, both patient awereness and referral, and

dermatology experience in dermoscopy are not adequately distributed on the territory. The statement is corroborated by the large number of melanomas diagnosed in advanced stages, and also the large number of benign lesions excised or biopsied to rule out a melanoma (low specificity of the method when performed by non-expert professionals).

In 2015 Vazques et al carried out a retrospective study involving 1073 cases of melanoma. The study population comprised patients diagnosed with melanoma between January 1997 and December 2011 at the Barretos Cancer Hospital, in São Paulo. This hospital is focused on public health and is a high-volume tertiary cancer centre, treating patients from all over the country. For this analysis the group excluded patients classified with in situ melanoma, and the clinical stage was determined using the 2009 UICC TNM system. Among the 1073 cases of melanoma included in the study, **27.6%** were classified as stage I, **25.3%** as stage II, **19.9%** as stage III and **15.7%** as stage IV – **35.6%** corresponding to thick melanomas. Regarding 5-year disease specific survival rate according to clinical stage, those classified as stage I had 91.4% of reaching 5-year free of the disease, those at stage II had 70.1%, at stage III 46.5% and patients at stage IV had 26.1%. Taking into account the high number of melanomas diagnosed in advanced stage, the overall 5-year survival rate for all patients included in the study was 67.6%. The authors compared their findings with those from developed countries in which there are successful secondary skin cancer prevention policies. Those developed countries achieved an overall survival rate higher than 90%, whereas in Brazil the survival rate is much lower. It leads the authors to suggest that the high prevalence of advanced cases in Brazil may be denoted by a lack of public health policies and failures in local strategies aiming the early diagnosis of this type of cancer.[2]

In 2018, de Melo et al published the largest Brazilian study in the identification of melanoma signature in Brazil. The group aimed to describe melanoma epidemiology, incidence and mortality in the country. For the study they accessed data from Brazilians

Hospital Cancer Registries, Population Based Cancer Registries and the National Mortality Information System. To calculate the incidence, data from the Brazilian Population Based Cancer Registries were obtained between the years 2000 and 2013. From the database searched, a total of 28624 patients diagnosed with melanoma were included. From all cases 47.3% were from the Southeast region of Brazil and 33.7% from the South region, encompassing 81% of all melanomas in the country. Regarding clinical stage (TNM), **32%** corresponded to stage I, **21.2%** to stage II, **20.6%** to stage III and **26.1%** to stage IV – **46.7%** corresponding to thick melanomas. For some reason the group did not include in the study patients diagnosed with in situ melanoma, except if it corresponded to a lentigo maligna which accounted for a total of 549 patients (1.9%).

In the same study, the group evidenced also the long waiting time for the first treatment since clinical diagnosis was done: 64.8% waited 30 or more days, and 23.6% had to wait at least 90 days. The authors suggested that the high proportion of advanced cases could be correlated to a deficient knowledge of the population regarding melanoma, non recognition of suspicious lesions by physicians (contributing to delays in diagnosis) and long waiting times for medical assistance. Besides they proposed an evaluation of feasibility and trade-offs of public health and behavioral counseling interventions focusing on promoting skin cancer prevention. [19]

According to the articles cited, the deficiency in prevention and early diagnosis of melanoma in Brazil is evident. Moreover, Xavier et at based themselves on a questionnaire to understand the delay in cutaneous melanoma diagnosis in Brazil. During the questionnaire it was observed that 41.7% of the patients had self-discovered melanoma on themselves while healthcare providers detected 29.9%. Besides, only 31.3% of the patients considered it was a serious skin malignancy as most of them thought the specific pigmented lesion was of no

importance. Furthermore 14.7% received improper treatments (destructive therapies) without a histopathological evaluation of the lesion. [103]

Once the disease progresses and reaches advanced stages (when lesions can not be surgically resected and / or is classified as metastatic) systemic therapy is considered. Nowadays dacarbazine is the gold standard chemotherapic in Brazil for patients with metastatic melanoma. [104,19] This chemoterapic is used at the dose of 1000 mg/m^2 (250 mg/m^2 for 5 days) through intravenous application every 21 days until the progression of the disease or uncontrolled treatment intolerance. Although it is the gold standard antineoplastic drug for metastatic melanoma in the Country, current studies show response rates around 5 – 12%.[105,106] A systematic review of 41 randomized clinical trials refered that most responses are transient, and only 1 – 2% of patients have a long-term response. [107] Besides the low rate response, the cost of this therapy is considered high for the SUS.

Considering that costs dramatically increases with disease stage and that in Brazil there is a high number of melanomas diagnosed in advanced stages, and considering the huge percentage of the brazilian population assisted by SUS, the interest in the amount of money spent with melanoma therapies also increases.

In 2009, Souza et al did a study in the estimate of direct cost of diagnosing and treating melanoma at different stages in São Paulo (Brazil), between the years 2000 and 2007. First of all, the authors searched in the database of Fundação Oncocentro de São Paulo the percentage of patients classified in each clinical stage. A total of 3187 cases were identified, but only 2740 were included in the study because they were already classified into stages (0, I, II, III and IV) - 447 cases were excluded because they were not staged. To calculate the cost, authors considered the standard procedures for diagnosis, management and follow-up of patients with melanoma, the costs with medical visits, laboratory tests, excision biopsy, histopathology examination, imaging exams for staging (X Ray, CT Scan), surgical

procedure, pre-surgical tests; medication-based treatment of melanoma (interferon for stage III, chemotherapy for stage IV), and palliative radiotherapy in stage IV. In cases when stage was different from 0, another surgical procedue for margins was also considered. As the target of the study was to estimate the direct cost of therapy of melanoma in different stages, the authors considered 1 year as the timeline for treatment and follow-up, without considering the possibility of deaths during that time. As results they found that with the cost amount spent to treat 1 patient in stage III, 81 in stage 0 or 40 in stage I could be treated; and the cost amount spent to treat 1 patient in stage IV could be used to treat 84 patients in stage 0 or 42 in stage I. It means that to treat stages III and IV SUS had to spend much higher costs. [108]

Following the world breakthroughs in therapies for melanoma in advanced stages, Guerra et al did a study about the cost-utility of targeted therapies compared to dacarbazine (the gold standard chemotherapic in Brazil) for the treatment of non-surgical melanoma and metastatic ones. The mean cost for dacarbazine was R$ 5,662.50 ($ 1,490.13) and much higher for targeted therapies (vemurafenibe, dabrafenibe, vemurafenibe/cobimetinibe and dabrafenibe/trametinibe) – ranging from R$ 167,461.70 ($ 44,068.87) for dabrafenib to R$ 425,901.00 ($ 112,079.21) for vemurafenib/cobimetinib. In this study authors affirmed the incorporation of targeted therapies in the Brazilian public health system would produce an additional spent of at least 19 times the national GDP per capita to increase in 1 year the quality adjusted survival of each patient with advanced/metastatic BRAF-mutant melanoma. As conclusion, they considered dacarbazine is more cost-useful for SUS in Brazil. [9,1] Taking into account the low response rates of this drug – that is considered as gold standard in Brazil – and the high percentage of cases diagosed in advanced stages, one can infer a high mortality rate in the Country due to melanoma diagnosed in advanced stages.

C. COMPARISON BETWEEN MODENA AND BRAZIL CAPABILITY TO DIAGNOSE MELANOMA:

According to the percentages of melanomas diagnosed in each clinical stage (0, I, II, III and IV) and considering that for a higher 5-year survival rate this malignancy should be diagnosed at stages 0, I and II, we note in Modena after the incorporation of RCM in the dermatologic department, there was a change in the scenario, with an improvement of diagnostic accuracy.

This improvement is demonstrated by comparing Modena model 1 with Modena model 2. We note that the total percentage of melanomas diagnosed as in situ or thin increased after the incorporation of RCM technology in respect to dermoscopy examination alone (86.1% vs 92.5%, respectively). Comparing only the amount of cases diagnosed at stage 0, we see a great increment of melanomas diagnosed as in situ (28.8% vs 40.3%, respectively) – which offers a much better outcome, with zero probability of tumor progression, to the patients. On the other hand, evaluating stages considered as thick melanomas (III and IV) we note a reduction of almost 50% in the percentage of melanomas classified in advanced stages (13.9% vs 7.5%, respectively).

Taking into consideration the largest Brazilian study in the identification of melanoma signature in Brazil made by de Melo et al, [19] and comparing to Modena model 1, it is evident there are differences in capacity to diagnose melanoma only through dermoscopic examination. The statement is supported by the huge differences in percentages of melanomas classified in each stage in Modena and in Brazil, also excluding for the Modena model 1 in situ melanomas: stages I and II (80.5% vs 53.2%, respectively) and stages III and IV (19.5% vs 46.7%, respectively).

If we consider Modena model 2, without in situ melanomas, as the example model that a system should adopt, this difference is even more discrepant: stages I and II (87.4% vs

53.2% - Modena model 2 vs Brazil, respectively), and stages III and IV (12.6% vs 46.7% - Modena model 2 vs Brazil, respectively).

D. ECONOMIC COST-EFFECTIVENESS ANALYSIS

From the patient's perspective, we performed a static mathematical modeling for economic evaluation in the form of a decision tree, in which all assumptions, effectiveness of the interventions analyzed, probabilities of outcomes and costs were drawn from publications that mostly approximate to the Brazilian reality. For this, the strategy used to produce the data imputed in the decision tree as well as information bases on epidemiology and costs of diagnosis and treatment of cutaneous melanoma were searched in the literature, and also consulting clinics. This way it was possible to describe the Brazilian model of skin cancer screening and melanoma diagnosis.

This economic cost-effectiveness analysis was performed according to the recommendations of the Brazilian Economic Evaluation Directive of the Ministry of Health.[b]

Base Case: The base case was composed by the scenarios of interest for the economic analysis – the reference one which uses dermoscopy for the diagnosis of melanoma, and the alternative one which uses RCM for second-level evaluation.

The reference scenario is the one we find in public health system in Brazil (SUS), while the alternative scenario is the one that uses RCM. Although already available in Brazil, RCM is used only in private clinics. Therefore, it is not included in the list of technologies incorporated by SUS or the National Agency of Supplementary Health.

- Reference scenario: Patients are evaluated with dermoscopy. If the dermoscopic patterns are highly consistent with skin cancer, patients are referred for complete excision followed by histopathology evaluation. On the other hand, if dermoscopic criteria are not specific for malignancy or if there is any doubt about the nature of the lesion, patients are

referred for punch biopsy followed by histopathology evaluation. If histological report is consistent with malignancy, then patient is submitted to total excision.

- Alternative scenario: Patients are firstly evaluated with dermoscopy. If based on dermoscopic criteria dermatologists are not sure about the possibility of a skin malignancy, patient is referred for a secondary evaluation with RCM. If RCM features are consistent with the malignancy, patient is referred directly to complete excision of that lesion followed by histopathlogy evaluation. In the alternative scenario punch biopsy is skipped most of the times, except in special cases as for example facial lesions (where even when a punch biopsy is performed it is guided by RCM features).

The technologies evaluated were dermosocpy and RCM. The measurement of effectiveness of interventions / technologies was estimated based on the diagnostic accuracy of each considering the percentage of specificity. The early diagnosis was the outcome of interest of the economic evaluation.

Regarding the costs imputed in the model, it should be noted that the one related to RCM was estimated after a phonecall consultation with a dermatologic clinic located in the city of São Paulo, in Brazil. For the private cost they charge are included the exam, dermatologist honoraria, and the necessary supplies for the examination.

• Economic analysis

The cost-effectiveness evaluation was structured based on the recommendations of the Ministry of Health's Economic Assessment Directive and was chosen in this thesis, as it is the most appropriate type of EAH to answer the objective of the research - as it aimed to compare costs and consequences of two health technologies, in terms of health benefits, thus being characterized as a complete economic analysis. [f]

[f] http://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf

Thus, the design of this cost-efectiveness analysis was based on a static mathematical model, the decision tree. We chose the decision tree because of its simplicity for deterministic analyzes, considering the time available for the conclusion of the study and the possible difficulties to estimate different transition probabilities between the various possible transitional states. The entire analysis and graphics were performed with the aid of TreeAge Pro® 2019 software.

• Study Perspective

The perspective of the analysis considered the patient as paying for the services provided for the diagnosis of melanoma. It should be noted that treatment costs were estimated considering the variation of costs for SUS and those for health insurance.

Willingness to pay threshold was set to 1 GDP per capita, which in Brazil corresponded to R$ 32,747.00 in 2018, according to the IBGE (the Brazilian Institute of Geography and Statistics).

• Time horizon

The time horizon applied was 01 (one) year because it is adequate to the proposed objectives, being considered enough to evaluate the costs and health consequences related to the scenarios evaluated and their respective strategies for the diagnosis and treatment of melanoma in Brazil.

• Identification, Measurement and Valuation of Costs

In the composition of the costs for diagnosis and treatment of melanoma in the base case, we considered the prices of inputs, drugs and medical honoraria. Only direct medical costs were considered.

The costs imputed in the model were estimated using the macrofinancing technique, which considers as total costs the amount paid for a "package" of services, in which everything considered necessary for the diagnosis and treatment of melanoma is already included in the final cost.

In the composition of the costs for dermoscopy and RCM we considered, in addition to medical honoraria: the cost of biopsy followed by excision, when opting for dermoscopy; and the cost of only excision, when opting for RCM. To estimate the cost of skin biopsy and skin tumor excision, we used those established by the Brazilian Medical Association (Associação Médica Brasileira - AMB) for the year 2018 - such as codes 54010098 - Skin and Mucosa Lesion Exeresis (Tumor) and 26030128 - Biopsy Skin Tumors, Superficial Tumors, Subcutaneous Cell Tissue, etc.

The cost for 1 RCM examination, as previously stated, was estimated considering the market price in 2019, in a private clinic located in the city of São Paulo. There the cost of the exam ranges from R$ 1,300 to R$ 2,300.

To estimate the treatment costs of melanoma, we used the study of Souza et al, [108] in which a total cost for melanomas diagnosed at an early stage were estimated as R$ 33,012,725.10 for the SUS and R$ 76,133,662.80 for health insurances. In the study the initial stages 0, I and II (considered in the model of the decision tree as "early diagnosis") comprised approximately 4.2% of the total cost of SUS used to treat melanomas and 1.3% of the total cost health insurances used to treat melanomas; whereas stages III and IV (considered in the model of the decision tree as "late diagnosis" or advanced stages) represent 95.8% and 98.7% of the total cost in both, respectively. Cost items were expressed in Reais and in unit values.

• Time Adjustments

Even considering that the cost data were from a period prior to the execution of this CEA, we chose not to apply fees to adjust these values for the present study, which will certainly be done in the future, for the budgetary impact analysis that will be done as complementation of the results of the present thesis. We opted not to make these adjustments at this time, considering that the costs found in this analysis are already above the reimbursement values for SUS.

- Cost-effectiveness analysis Assumptions

Table 1 presents the assumptions assumed in the analysis and their respective estimated variations, considering the base case, the strategies analyzed and the outcomes of interest.

Description	Minimum	Maximum	Average	Standard Deviation	Source
Costs for reflectance confocal microscopy: considered those charged in the private practice	R$ 1,300.00	R$ 2,300.00	R$ 1,800.00	R$ 707.106	Private clinic in the city of São Paulo - 2019
Costs for dermoscopy: including the cost of biopsy* and tumor excision **	* R$ 100.00 **R$ 250.00	* R$ 400.00 **R$ 550.00	* R$ 175.00 **R$ 475.00	* R$ 106.066 **R$ 106.066	Private clinic in the city of São Paulo - 2019
Costs to treat early stage melanoma	R$ 38.284	R$ 1,138.13	R$ 76.706	R$ 534.070	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Costs to treat late stage melanoma	R$ 30,969.67	R$ 32,054.23	R$ 31,511.95	R$ 766.899	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Reflectance confocal microscopy effectiveness	0.75	0.82	788	0.0494	Xiong YQ et al. Comparison of dermoscopy and reflectance confocal microscopy for the diagnosis of malignant skin tumours: a meta-analysis. J Cancer Res Clin Oncol. 2017;143:1627-1635.
Dermoscopy effectiveness	0.45	0.53	491	0.0565	Xiong YQ et al. Comparison of dermoscopy and reflectance confocal microscopy for the diagnosis of malignant skin tumours: a meta-analysis. J Cancer Res Clin Oncol. 2017;143:1627-1635.
Probability of early diagnosis: stages 0, I and II	212	0.32	266	0.0763	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of late diagnosis: stages III and IV	206	261	233	0.0388	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of access to treatment	0.92	926	923	0.0042	DATASUS http://datasus.saude.gov.br/informacoes-de-saude/tabnet/epidemiologicas-e-morbidade
Probability of cure in early diagnosis	701	914	807	0.1506	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of cure in late diagnosis	261	465	363	0.1442	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of cure without treatment	86	299	192	0.1506	Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of death from other causes	1 minus the probability of cure in early diagnosis				Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.
Probability of disease regression	1 minus the probability of cure in late diagnosis				Souza RJSP, et al. An Bras Dermatol. 2009;84:237-43.

Table 1: Assumptions assumed in the analysis and their respective estimated variations, considering the base case, the strategies analyzed and the outcomes of interest.

E. DECISION TREE

Decision Tree Structure: In the present study, the decision tree represents the two scenarios evaluated in the base case. The structure of the model (**Figure 2**) is based on two decision nodes (dermoscopy and RCM), each representing one scenario (the reference or the alternative scenario) and mutually excluders for the diagnosis of melanoma. Each may allow the physician with different probabilities to make an early diagnosis of melanoma - in this study considered as stages 0, I and II, or late diagnosis - considered in this study as stages III and IV, when tumor is classified in advanced stage.

The model also presents 6 chance nodes. Probabilistically these nodes considered that regardless of the stage in which a melanoma is diagnosed (early or late diagnosis), it is possible that the patient is treated or not (with or without treatment), whether by personal decision or difficulty in accessing a health care assistance.

Finally, whether the tumor is treated or not, the patient could still stay alive (live) and die from other causes, or progress to metastasis (disease progression) and die as a result of disease progression. Since the model is not dynamic, there is no possibility for the patient to transit through the possible health states inherent in the natural history of melanoma.

Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 2: Decision tree structure showing the two decision nodes, representing both base case scenarios and the 6 chance nodes.

Despite being simple but capable of portraying the scenario of skin cancer in Brazil, the objective of this structure is to get as close as possible to the national reality, so that we can evaluate the costs and consequences of early diagnosis of melanoma, using the best available technologies at the lowest possible cost. This way helping to improve allocative resource efficiency in the health sector by using better evidence to inform decisions in the process of incorporating health technologies.

• Decision Tree Imputed Variables

Table 2A and **Table 2B** show the variables that parameterized the decision tree in TreeAge Pro® 2019 software.

VARIABLES	DESCRIPTION
C_BIOPSY	Cost of a punch biopsy
C_DERMATOSCOPY_EXAM	Cost of dermatoscopy examination during dermatologic visit
C_CONFOC_EXAM	Cost of inputs for reflectance confocal microscopy examination
C_EXERESIS	Cost of complete exeresis of the tumor
C_EARLY_TREAT	Cost of treatment without metastasis
C_LATE_TREAT	Cost of treatment in advanced stages
E_CONFOC_EXAM	Reflectance confocal microscopy effectiveness
E_DERMATOSCOPY	Dermatoscopy effectiveness
P_TREAT_ACCESS	Probability of access to treatment
P_CURE_EARLY_DIAG	Probability of cure in early diagnosis
P_CURE_LATE_DIAG	Probability of cure in late diagnosis
P_CURE_NO_TREAT	Probability of cure without treatment
P_EARLY_DIAG	Probability of early diagnosis
P_LATE_DIAG	Probability of late diagnosis

Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Table 2A: Variables that parameterized the decision tree and their respective descriptions.

NAME	DESCRIPTION	TYPE	ESTIMATED VALUE
D_E_CONFOC_EXAM	Distribution of effectiveness of reflectance confocal microscopy	Beta	0,785
D_P_CURE_NO_TREAT	Distribution of probability of cure without treatment	Beta	0,1925
D_P_TREAT_ACESS	Distribution of probability of access to treatment	Beta	0,923
D_P_LATE_DIAG	Distribution of probability of late diagnosis	Beta	0,2335
D_P_CURE_EARLY_DIAG	Distribution of probability of cure in early diagnosis	Beta	0,8075
D_C_EXERESIS	Distribution of the cost of complete excision	Gamma	475,0
D_C_EARLY_TREAT	Distribution of the cost of early treatment	Gamma	767,06
D_E_DERMATOSCOPY	Distribution of effectiveness of dermatoscopy	Beta	0,49
D_C_BIOPSY	Distribution of the cost of biopsy	Gamma	175,0
D_C_LATE_TREAT	Distribution of the cost of late treatment	Gamma	31512,0
D_P_EARLY_DIAG	Distribution of probability of early diagnosis	Beta	0,266
D_C_DERMATOSCOPY_EXAM	Distribution of the cost of dermatoscopy examination during a dermatologic visit	Gamma	455,0
D_P_CURE_LATE_DIAG	Distribution of probability of cure in late diagnosis	Beta	0,363
D_C_CONFOC_EXAM	Distribution of the cost of reflectance confocal microscopy examination	Gamma	1800,0

Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Table 2B: Distribution of the variables that parameterized the decision tree for probabilistic analysis and sensitivity analysis.

F. COST-EFFECTIVENESS ASSESSMENT RESULTS

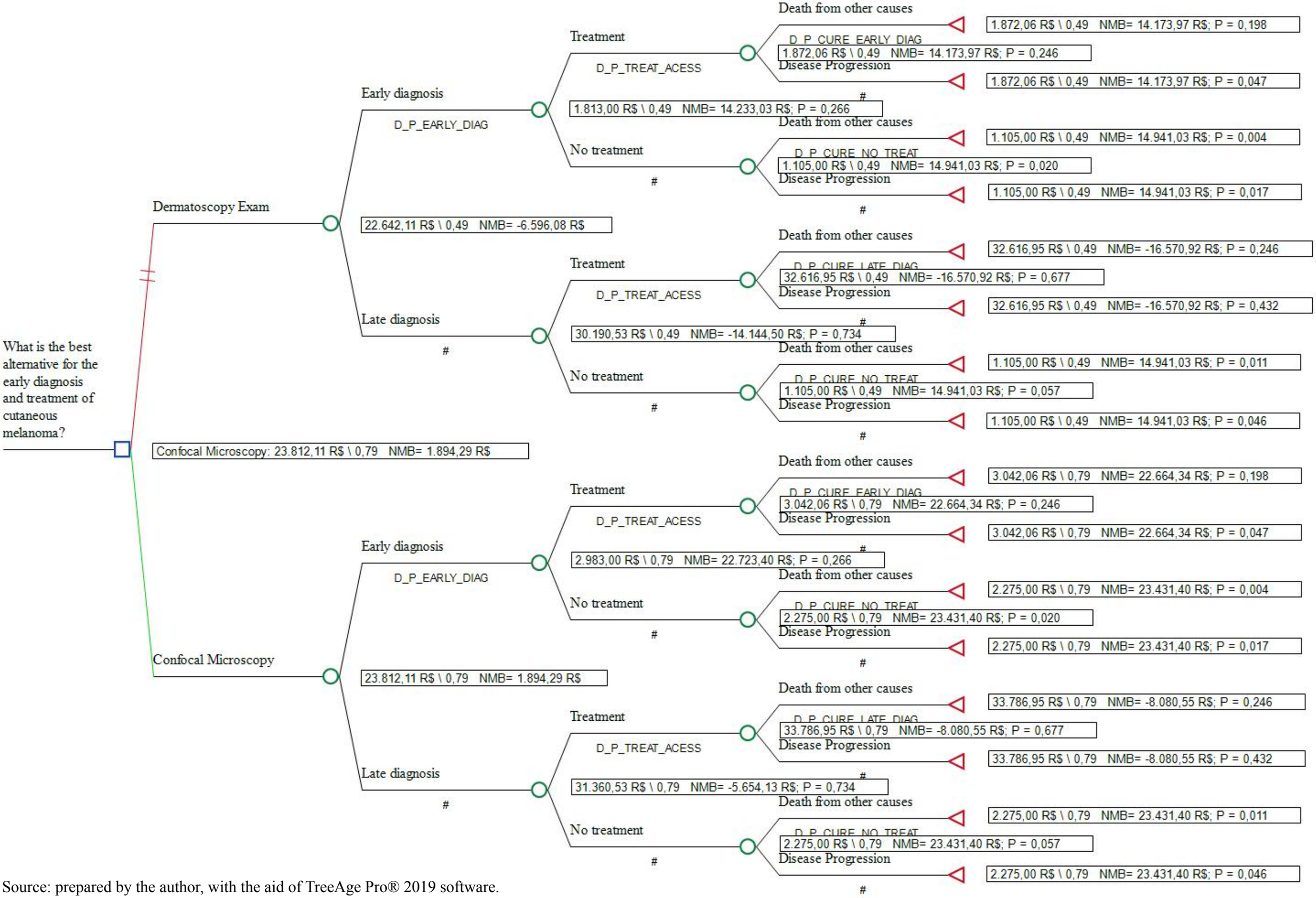
The results of this CEA were expressed by the Incremental Cost-Effectiveness Ratio (ICER), obtained by calculating **ICER = (C1 - C2) ÷ (E1 - E2)**. [g] The ICER was presented in the cost-effectiveness plan, aiming to verify the existence of a dominant and dominated strategy, depending on the willingness to pay threshold, defined in the model.

The determination of the cost-effectiveness strategy was also based on the net monetary benefit (NMB), which is a method based on the combination of cost, effectiveness and willingness to pay threshold. NMB is calculated using the **equation NMB = (E x λ) - C**, where E corresponds to the effectiveness of the technology in question, λ corresponds to the willingness to pay threshold and C corresponds to the cost of the technology in question. [109]

The expression (E x λ) identifies how much the prospect is willing to pay for the amount of benefit generated, and the subtraction of this expression by C shows how much it would be saved or spent to use the technology, i.e it allows to quantify the net benefit in monetary values for each strategy. Thus if NMB is positive, the intervention is considered cost effective; otherwise, the NMB will be negative. [109]

Considering the decision tree's Roll Back (**Figure 3**) we find that the diagnosis using confocal microscopy is cost-effective.

[g] http://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 3: Decision tree after Roll Back. Roll Back of the decision tree showing all costs, including the incremental, the effectiveness, the incremental cost-effectiveness ratio and the net monetary benefit.

The model predicted that at a cost / patient of R$ 23,812.11 it would be possible to achieve an effectiveness of 0.785 in the diagnosis and early treatment of cutaneous melanoma (**Figure 4**). The estimated incremental cost-effectiveness ratio was R$ 3,966.10 which means that in order to obtain one more unit of effectiveness (1% more in the diagnostic capacity of RCM), this value would have to be disbursed, which is within the willingness to pay threshold of the model.

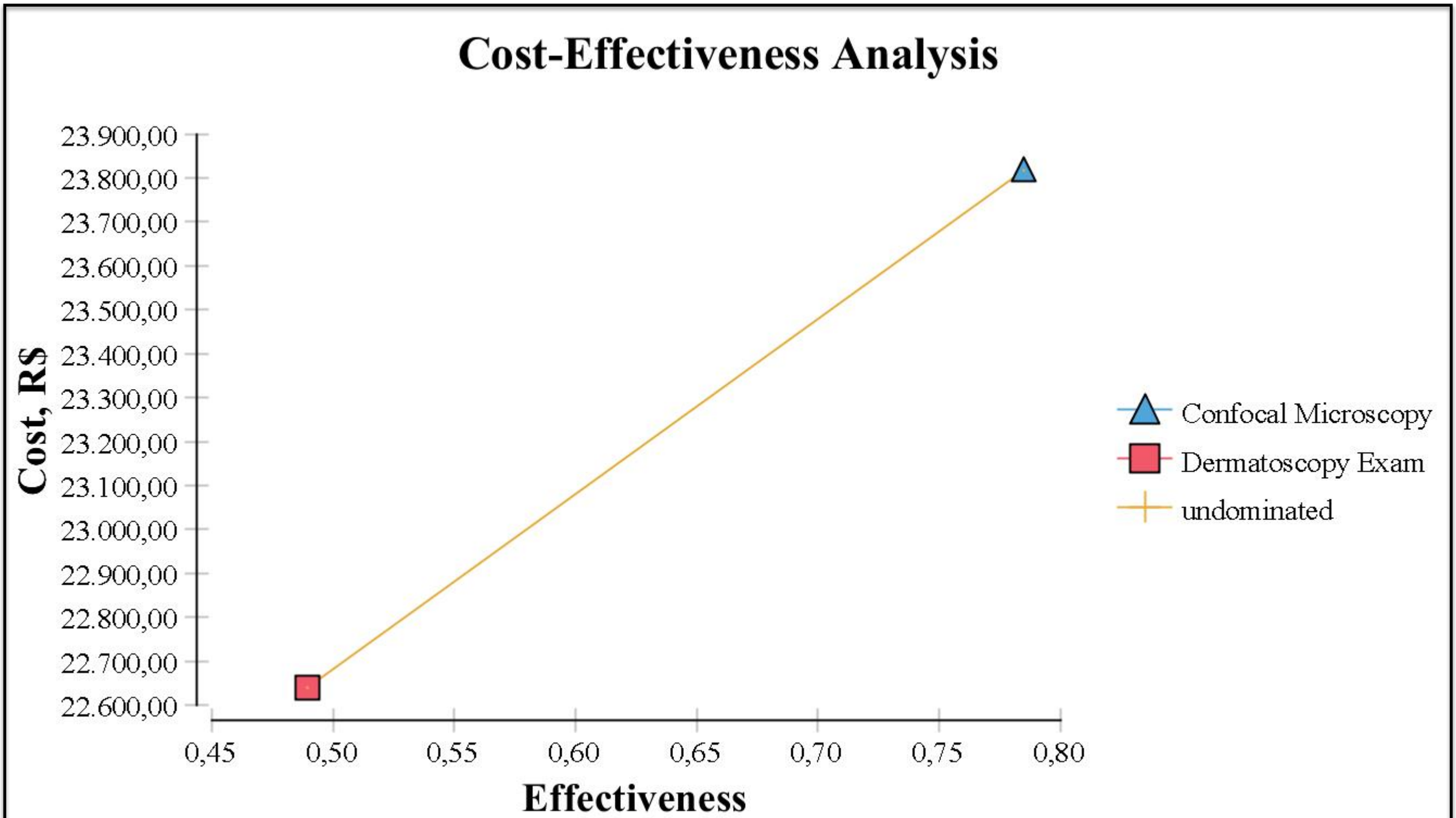
The net monetary benefit showed a positive value of R$ 1,894.29 for RCM examination, what means that each patient diagnosed and treated early would enable a return on invested capital in the order of NMB. Unlike in dermatoscopy NMB showed a negative value (- R$ 6,596.08), which means loss of resource.

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E
Dermatoscopy Exam	R$ 22,642.11	R$ 0.00	0.49	0	R$ 0.00	-R$ 6,596.08	R$ 46,208.38
Confocal Microscopy	R$ 23,812.11	R$ 1,170.00	0.785	0.295	R$ 3,966.10	R$ 1,894.29	R$ 30,333.89

Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 4: Summary of the Roll Back results of the decision tree: it is possible to know the costs, including the incremental costs (Incr Cost), the effectiveness (Eff), the incremental effectiveness (Incr Eff), the incremental cost-effectiveness ratio (ICER), the net monetary benefit (NMB) and the cost-effectiveness ratio (C/E).

The cost-effectiveness plan (**Figure 5**) showed that the dominance of confocal microscopy is not absolute in relation to dermoscopy. The yellow line linking the two strategies reveals that either alternative could be cost effective, depending on the willingness to pay threshold.



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 5: Cost-effectiveness plan. On the vertical axis we have the costs and on the horizontal, the effectiveness.

• Sensitivity Analysis

Only the parametric uncertainties, which are related to the values of the assumed and imputed variables in the decision tree, were analyzed. Thus the robustness of the model was assessed from deterministic univariate and probabilistic multivariate sensitivity analysis using TreeAge Pro® 2019 software.

The deterministic univariate analysis were performed using a tornado diagram, where the sensitivity analysis of the cost variables were presented simultaneously, as well as any other variable that could impact the analysis result. Considering that the data came from samples, the limits used for variation of parameter were those of the estimate the confidence interval.

Probability multivariate analysis was performed using second order Monte Carlo simulations, with a total of 10,000 simulations. Gamma distribution was used for cost variables and Beta for effectiveness probabilities. The α (alpha) and λ (lambda) values of the Gamma distributions, as well as the α (alpha) and β (beta) values of the Beta distributions were estimated from the means and standard deviations of the variables used in the analyzes.

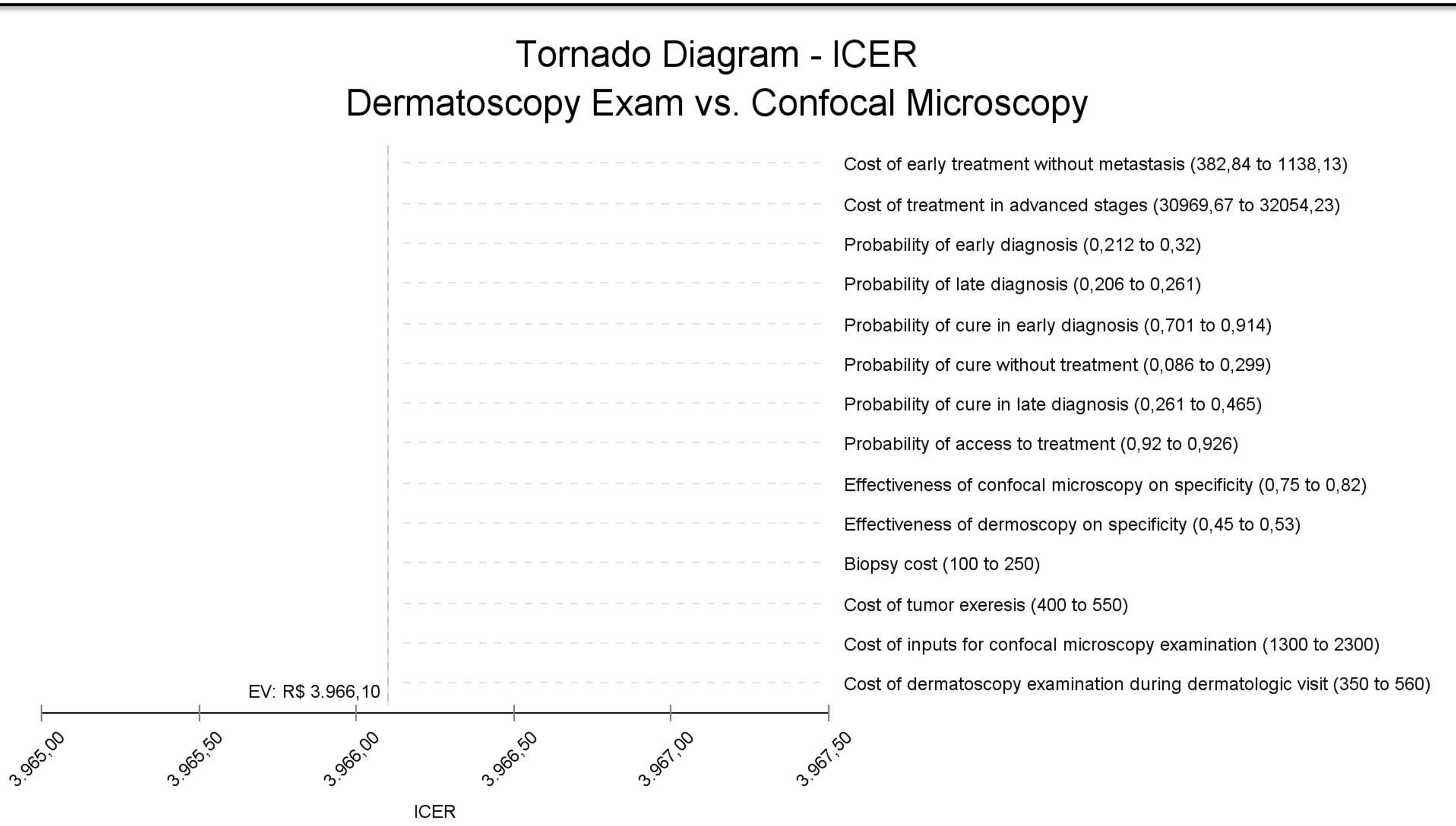
Data were presented using cost-effectiveness scatterplots (to show simulations in the four quadrants of the cost-effectiveness plan) and cost-effectiveness acceptability curves (for the purpose of showing, according to predetermined willingness to pay values, what percentage of the simulations would have results considered cost-effective).

• Deterministic Sensitivity Analysis

Expected values of both, the Incremental Cost-Effectiveness Ratio (**Figure 6**) and the net monetary benefit (**Figure 7**), were not sensitive to parametric variations (which can be observed in the graph due to the absence of horizontal bars – tornado aspect – in each

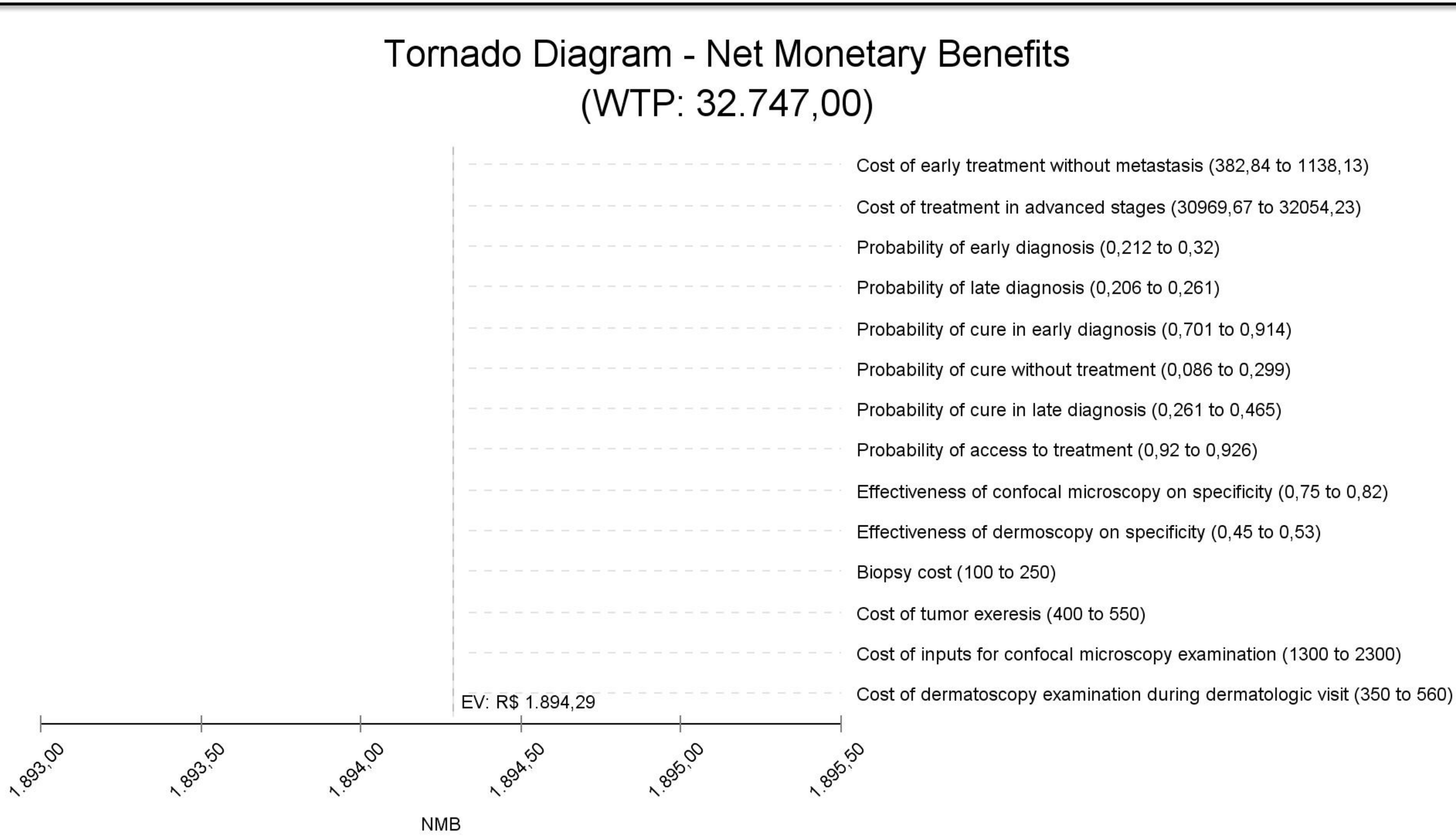
parameter analyzed), when submited to deterministic univariate sensitivity analysis, attesting the robustness of the model and the confidence in its results.

Thus it is believed that no further evaluation would be necessary by performing the deterministic bivariate analysis.



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 6: Tornado Diagram of Incremental Cost-Effectiveness Ratio.



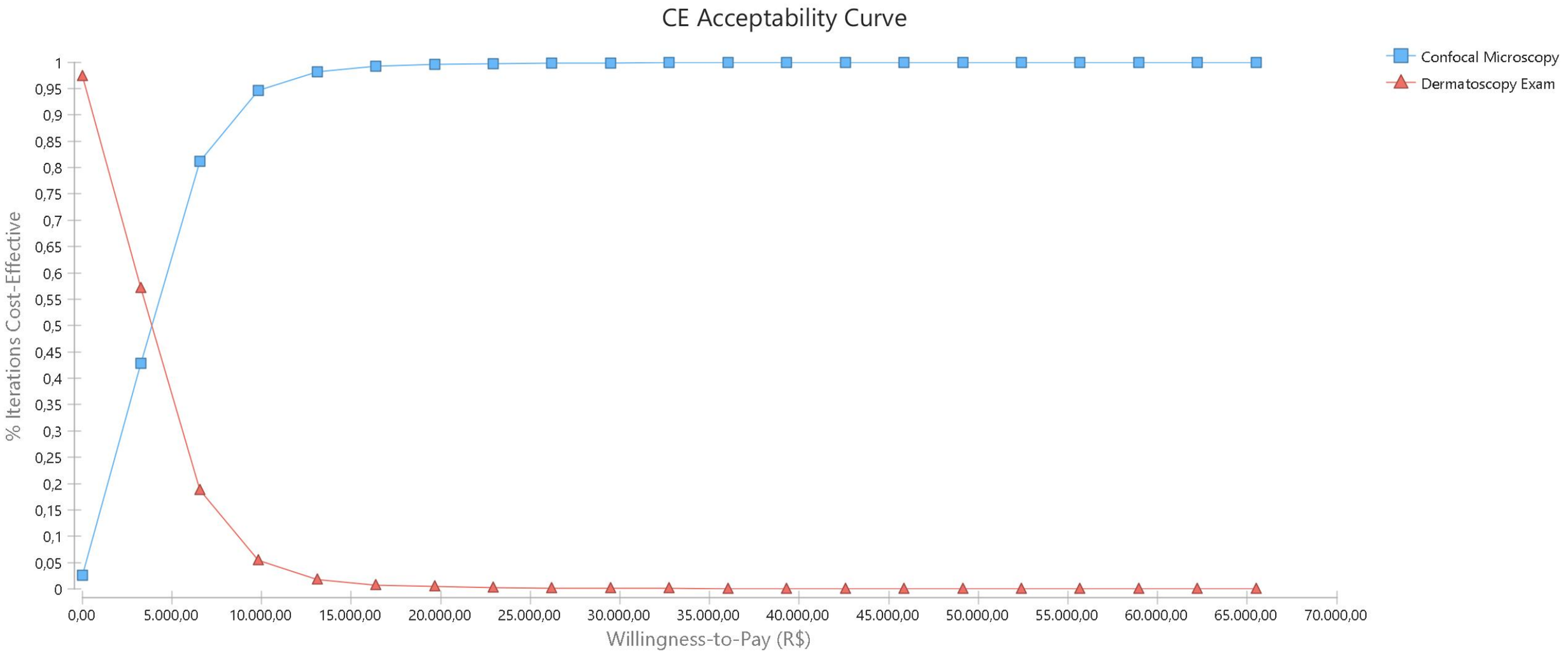
Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 7: Tornado Diagram of Net Monetary Benefit.

• Probabilistic Sensitivity Analysis

As mentioned, in the probabilistic sensitivity analysis 10,000 Monte Carlo simulations were performed to address the uncertainties related to the variability of the imputed parameters in the decision tree model.

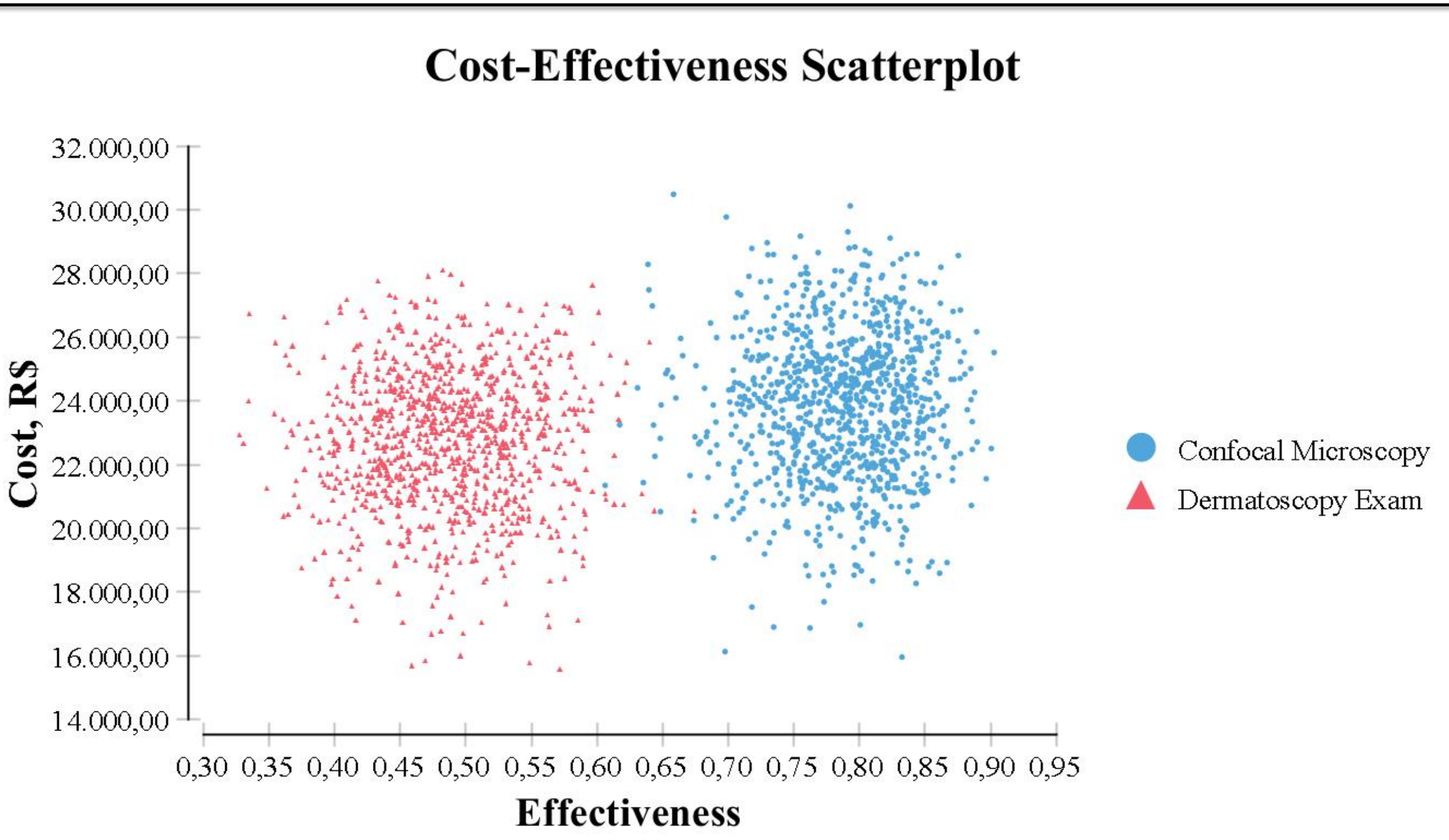
The cost-effectiveness acceptability curve (**Figure 8**) shows there is no change in thresholds, regardless of the increase in willingness to pay thresholds.



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 8: Cost-effectiveness acceptability curve.

Cost-effectiveness scatterplot (**Figure 9**) shows there was less cost dispersion in relation to effectiveness (or higher concentration) in reflectance confocal microscopy, and greater dispersion in dermoscopy. Cost dispersion remained within the willingness to pay threshold.



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

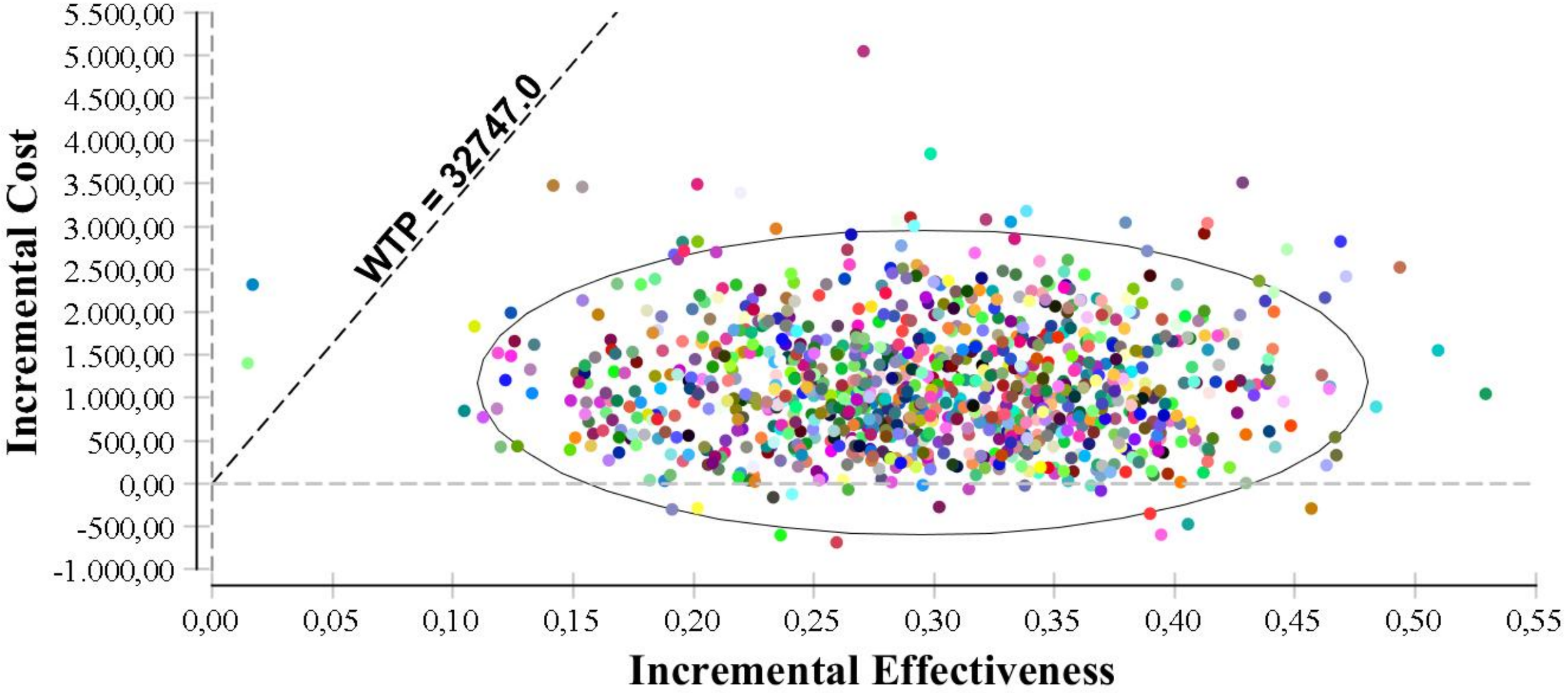
Figure 9: Cost-Effectiveness Scatterplot.

In the incremental cost-effectiveness scatterplot plot (**Figures 10 and 11**), reflectance confocal microscopy was compared to dermoscopy. The 95% confidence interval is represented by the ellipse. The willingness to pay threshold was 1 GDP per capita and the iteration (or repetition) rate was 1: 10,000. The graph shows smaller dispersions, and therefore higher concentrations of iterations of the evaluated scenarios, both in relation to incremental cost (Y axis) as well as in relation to incremental effectiveness (X axis) in the 10,000 second-order Monte Carlo simulations performed. Higher concentration of iterations are seen in quadrant I, which may be favorable to confocal microscopy. In quadrant I, we have the most expensive but most cost-effective technologies.

In Quadrant IV, which corresponds to component C1 (representing 254 simulated iterations - 0.0254% of the 10,000 simulations), the effectiveness increment is greater than zero (EI > 0) and the cost increment is less than zero (CI < 0). Because it is considered "superior" (meaning the technology is cheaper and more effective), this quadrant corresponds to where simulated iterations are and in which RCM is superior or dominant over dermoscopy.

In the case of component C2 in Quadrant I (which corresponds to 9736 simulated iterations - 97.36% of the 10,000 simulations), the effectiveness increment is greater than zero (EI > 0) as well as the cost increment (CI > 0). But because it has a much lower incremental cost-effectiveness ratio than the willingness to pay, this component is also in favor of reflectance confocal microscopy.

Incremental Cost-Effectiveness, Confocal Microscopy v. Dermatoscopy Exam



Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 10: Incremental Cost-Effectiveness Scatterplot (iteration rate 1: 10,000).

Components	Quadrants	INCR EFF	INCR COST	ICER	Frequency	Percentage
C1	IV	IE>0	IC<0	Superior	254	0.0254
C2	I	IE>0	IC>0	ICER<32747.0	9736	0.9736
C3	III	IE<0	IC<0	ICER>32747.0	0	0
C4	I	IE>0	IC>0	ICER>32747.0	9	0.0009
C5	III	IE<0	IC<0	ICER<32747.0	0	0
C6	II	IE<0	IC>0	Inferior	1	0.0001
Indifferent	Origin	IE=0	IC=0	0/0	0	0

Source: prepared by the author, with the aid of TreeAge Pro® 2019 software.

Figure 11: Text report of incremental effectiveness (INCR EFF), incremental Cost (INCR COST), and incremental effectiveness ratio (ICER).

Summing the iterations of the simulated components that are located within the 95% confidence interval and below the willingness to pay threshold in the base case (components C1, C2) we reach a total of 9,990, which corresponds to 99.9% of all 10,000 simulations performed - favorable to reflectance confocal microscopy.

This way, the probabilistic sensitivity analysis using the Acceptability Curve and the incremental cost-effectiveness scatterplot helped to further reduce the uncertainties of the model, showing that the probability of RCM dominance over dermoscopy is greater for early diagnosis of melanoma.

5. DISCUSSION:

Considering that an early recognition of melanoma is directly correlated to a lower number of melanomas diagnosed in advanced stages, in Brazil we can conclude there is an overall poor capacity of the physicians to detect melanoma at early stages based on dermoscopic evaluation (general low expertise on dermoscopy in the country).

It has been demonstrated by many publications how RCM improves diagnostic accuracy of melanoma, overcoming dermoscopic evaluations. But, looking at the amount of cases diagnosed as stage III and IV in Brazil we can infer that, unfortunately, patient access, patient and doctor awerness, and dermoscopic skills are not well spread in the Country. The high demand for aesthetic procedures by the patients, and the great financial return obtained for such procedures are driven factors for a greater interest in aesthetics by dermatologists in Brazil, thus with only non-dermatology specialists and few dermatologists focused on skin cancer diagnosis. Besides, there is lack of health policies advertising alerting the population for the risks of skin cancer, specifically melanoma, in a way people would be more encouraged to search dermatologists for skin cancer screening, and there is not attention in GPs educational program on skin cancer recognition and prevention.

A general deficiency of the system in Brazil is revealed by a total of 46.7% of melanomas diagnosed in advanced stages, [19] a high lethality rate justified by the high number of deaths that has been estimated for the year 2008, [h] and a much lower overall 5-year survival rate in the country when compared to developed countries, [2] as for example Italy, herein represented by Modena.

If we take into account only dermoscopic knowledges, in Modena (Modena model 1) we see that even before the incorporation of RCM, dermatologists were already experts in the diagnosis of melanoma only with dermoscopy: 86.1% of melanomas diagnosed in early phase. In contrast, according to De Melo [19] in Brazil almost half of the cases were diagnosed in advanced stages (46.7%).

If we proceed along with technological advances and diagnostic improvements, the acquisition of RCM represents a huge increment in the diagnostic accuracy of skin cancer. From that point, if we compare the actual Brazilian scenario (keeping the data from De Melo,[19]) and we compare to Modena model 2, what we see is that Brazil is far from being an effective country in the diagnosis of melanoma.

Moreover, a late diagnosis implicates in the use of therapies other than complete excision, which enhances the expenses of the national health system. The actual model in Modena not only saves lives by diagnosing much more patients in early stages, but also lead to a saving of 260.000 Euros for each 1 million inhabitants examined only avoiding unnecessary excisions of benign moles. In the other hand, in the model analyzed in Brazil most of the costs with melanoma (over 95%) were attributed to treatments of advanced stage (III and IV), which demand high cost drugs (chemotherapy), with no effective benefits on the patient's health. Thus, the cost of treating 1 patient in advanced stage may cover several early stage treatments. Based on the capacity and high-level expertise of Modena to diagnose

[h] http://datasus.saude.gov.br/informacoes-de-saude/tabnet/epidemiologicas-e-morbidade

melanomas in early stages added to possible savings for the national health system, nowadays Modena model 2 is seen as a desired skin cancer model screening in the world.

This makes us wonder how prevention and early diagnosis are as important for saving lives as it is for financial reasons, especially for health system such as SUS in Brazil.

If we took into account only the considerable resource savings that could be generated for SUS, it would demand economic health assessment studies to assess, for example, the additional resources that could be applied to programs for the prevention and investment in teaching new techniques to potentialize the early diagnosis of skin cancer.

As in any cost-effectiveness assessment, especially when performed with mathematical models, our analysis has limitations and results may change if there are changes in the perspectives analyzed, in the parameters used or in the methodology of the analysis. In this study, the sensitivity analysis showed that the model is robust in Brazil.

Once an economic cost-effectiveness analysis has been completed, a budget impact assessment study is carried out, and it is up to the manager to decide whether or not to implement it, considering the economic viability. For this reason, it makes necessary the understanding of the willingness limit to pay, in order to assist the manager to maximize the benefit provided to patients within a given budget constraint.

Brazil does not yet have robust and consolidated studies from the perspective of value-based health pricing and has not officially adopted a willingness threshold to be paid. However, according to the methodological guidelines of the Ministry of Health, it is recommended that economic analysis include broad ranges of analysis in the acceptability curves, including one to three times the Country's GDP per capita. In this thesis we have considered 1 GDP per capita.

The cost-effectiveness threshold makes reference to the recommendation of the Macroeconomics and Health Commission of the World Health Organization, that states

technologies with ICERs below one GDP per capita are considered to be very cost-effective. Those with ICERs less than three times GDP per capita are considered cost-effective, and when ICERs are above three times GDP per capita technologies are considered non-cost-effective.

In this context, the results show that confocal microscopy may be the best alternative available, since the ICER is within the willingness to pay limit. It should be noted that, in the model, the cost of treatment was responsible for the greater monetary impact.

6. LIMITATIONS:

The proposed objectives were achieved, although we are aware of the limitations of the study, especially regarding analytical uncertainty, since dynamic models would be the most appropriate to analyze the costs and consequences of treating a melanoma patient. Dynamic models would take into account the probabilities defined by the natural history of the disease, the evolution in skin cancer screening, the effectiveness of the treatment in different clinical stages, the risks of complications, the competitive risks of mortality and the loss of income from death or morbidity, which are not possible to consider in the static decision tree model.

To establish a complete model would require a robust set of information on several variables, which we did not have available within the time frame for completion of the study. As a research agenda, it is committed to continue the studies with other designs of economic analysis in health, such as budget impact analysis and more reliable modeling with reality.

7. CONCLUSION

The economic impact of the diagnosis and treatment of cutaneous melanoma has been poorly evaluated in Brazil. Considering that both the incidence of skin cancer and the costs of treatment increase, it is fundamental for the Brazilian health system to be evaluated.

The model adopted in Modena shows how an adequate skin cancer screening impacts directly the percentage of melanoma diagnosed in early stages - what consequentely reduces the amount of cases classified as advanced. Moreover, the incorporation of reflectance confocal microscopy in daily practice in the Dermatology department as a second-level examination for doubtful lesions instead of sending them for punch biopsy (or even complete excision) lead to savings.

The thesis that emerged from this study is that reflectance confocal microscopy is cost-effective for early diagnosis of melanoma, and that incorporating this technology in Brazil may reduce the costs of this disease in SUS, the Brazilian health system.

Apart from all, brazilian dermatologists should be better trained in dermoscopy, health policies should raise population awareness about skin cancer (specially the risks of melanoma) and social programs should be encouraged in Brazil in order to educate the population to adequately protect themselves from the sun (taking into account the country's territorial location that promotes a year-round sun exposure).

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