PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

MURILO DE OLIVEIRA LIMA CARAPEBA

DERMATOSCOPIA: UMA TÉCNICA APLICÁVEL PARA A DIFERENCIAÇÃO ENTRE LENTIGO MALIGNO E LENTIGO MALIGNO MELANOMA? UMA REVISÃO SISTEMÁTICA DA LITERATURA

Presidente Prudente – SP
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Dissertação apresentada à Pró-Reitoria de Pesquisa e Pós-Graduação, Universidade do Oeste Paulista, como parte dos requisitos para obtenção do título de Mestre Mestre em Ciências da Saúde – Área de concentração: Ciências da Saúde.

Orientadora:
Profa. Dra. Gisele Alborghetti Nai

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Presidente Prudente, 19 de fevereiro de 2019.

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Dedicatória

DEDICATÓRIA

Não fazemos nada sozinhos, não é mesmo? E nem somente para nós mesmos, mas para os outros também. Por isso acho importante ter esse espaço aqui e começar por eternizar o sentimento na forma de palavras para algumas pessoas que foram importantes até aqui. Quero dedicar esta dissertação a todos que participaram da minha vida nesses últimos 2 anos, mas em especial quero dedicar à minha mãe Regina, que sei que se orgulha muito de cada conquista minha e dos meus irmãos. Quero dedicar esta dissertação à minha avó Ana, que desde sempre me apoiou na busca do sonho de ser médico e sempre está do meu lado, e ao meu avô Agripino, que não só ajudou a plantar a semente da medicina em mim, mas também a semente da humanidade e do amor ao próximo, no mais singelo sentido do “fazer o bem, sem olhar a quem”. E é por isso que termino por dedicar essa dissertação aqueles que um dia possam se beneficiar de seu conteúdo.

Agradecimentos

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“É impossível aprisionar os que tem asas”

Caio Fernando Abreu

Resumo

RESUMO

Dermatoscopia: uma técnica aplicável para a diferenciação entre lentigo maligno e lentigo maligno melanoma? Uma revisão sistemática da literatura

Introdução: O lentigo maligno melanoma (LMM) é um melanoma que surge da evolução do lentigo maligno (LM). Ambas as lesões podem ter tratamentos diferentes, por isso a distinção entre elas é fundamental para o planejamento terapêutico. **Objetivo:** Avaliar se a dermatoscopia é um método diagnóstico com boa acurácia para o diagnóstico e diferenciação entre LM e LMM. **Material e métodos:** Foi realizada uma revisão sistemática da literatura de estudos com grau de recomendação A ou B de acordo com o documento "Níveis de Evidência 1" do CEBM (*Center for Evidence-based Medicine*) que avaliaram comparativamente a dermatoscopia e a histopatologia do LM e LMM de pele. Utilizamos os seguintes descritores: dermatoscopia, lentigo maligno, lentigo maligno melanoma. A seleção dos estudos foi feita através da ferramenta QUADAS (*Quality Assessment of Diagnostic Accuracy Studies*)-2, recomendada para revisões sistemáticas de acurácia diagnóstica. **Resultados:** No período de 1996 a 2018, foram encontrados 224 artigos, dos quais 14 foram incluídos para análise qualitativa e 5 para meta-análise. O teste de Heterogeneidade (*I-square*) para a sensibilidade foi de 97,3% e para a especificidade de 92,8%. A sensibilidade agrupada foi de 0,74 (Intervalo de confiança - IC95%: 0,69-0,78) e a especificidade agrupada de 0,78 (IC95%: 0,74-0,82). O *I-square* para a Razão de verossimilhança (RV) positiva foi de 83,7%%, para a RV negativa foi de 96,1% e para *I-square* para *Odds ratio* diagnóstico (DOR) foi de 90,4%. A RV positiva agrupada foi de 3,68 (IC95%: 2,21-6,13), a RV negativa agrupada foi de 0,21 (IC95%: 0,07-0,60) e para DOR grupado foi de 28,20 (IC95%: 4,74-179,23). A área sob a curva (AUC) foi de 0,9082. Estruturas romboidais foi o critério dermatoscópico mais frequente associado à LM/LMM. **Conclusão:** Embora a dermatoscopia tenha boa acurácia no diagnóstico de lesões de LM e LMM, mais estudos são necessários para determinar se a dermatoscopia é capaz de diferenciar tais lesões.

Palavras-chave: lentigo maligno, dermatoscopia**,** diagnóstico, revisão sistemática, histopatologia.

ABSTRACT

Dermoscopy: a technique applicable to the differentiation between lentigo maligna and lentigo maligna melanoma? A systematic review

Introduction: The lentigo maligna melanoma (LMM) is a melanoma that arises from the evolution of lentigo maligna (LM). Both lesions have different treatments, so the distinction between them is fundamental for therapeutic planning. **Objective:** To evaluate whether dermoscopy is an effective diagnostic method for differentiating between LM and LMM. **Material and methods**: A systematic review of the literature of studies with A or B recommendation grade was performed according to the Center for Evidence-based Medicine's "Levels of Evidence 1", which compared the dermoscopy and histopathology of LM and LMM of skin. We used the following descriptors: dermoscopy, lentigo maligna, lentigo maligna melanoma. The selection of the studies was done using the QUADAS tool (Quality Assessment of Diagnostic Accuracy Studies) -2, recommended for systematic reviews of diagnostic accuracy. **Results:** Between 1996 and 2018, 224 articles were found, of which 14 were included for qualitative analysis and 5 for meta-analysis. The Heterogeneity test (I-square) for the sensitivity was 97.3% and for the specificity of 92.8%. The pooled sensitivity was 0.74 (Confidence Interval - 95% CI: 0.69-0.78) and the pooled specificity was 0.78 (95% CI: 0.74-0.82). The I-square for positive likelihood ratio was 83.7%, for negative RV was 96.1% and for I-square for diagnostic Odds Ratio (DOR) was 90.4%. Grouped positive RV was 3.68 (95% CI: 2.21-6.13), group negative RV was 0.21 (95% CI: 0.07-0.60) and for group DOR was 28.20 (95% CI: 4.74-179.23). The area under the curve (AUC) was 0.9082. Rhomboid structures were the most frequent dermoscopy criterion associated with LM / LMM. **Conclusion:** Although dermoscopy has good accuracy in the diagnosis of lentiginous lesions, further studies are needed to determine whether dermoscopy is able to differentiate LM from LMM.

Keywords: lentigo maligna, dermoscopy, diagnosis, systematic review, histopathology.

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É POSSIVEL DIFERENCIAR LENTIGO MALIGNO DE LENTIGO MALIGNO MELANOMA POR DERMATOSCOPIA? UMA META-ANÁLISE.

IS IT POSSIBLE TO DIFFERENTIATE LENTIGO MALIGNO FROM LENTIGO MALIGNO MELANOMA BY DERMOSCOPY? A METANALYSIS.

Título resumido: **DERMATOSCOPIA PARA LENTIGO MALIGNO**

Running title: **DERMOSCOPY FOR LENTIGO MALIGNO**

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RESUMO

Introdução: O lentigo maligno melanoma é um melanoma que surge da evolução do lentigo maligno. Ambas as lesões têm prognósticos diferentes, por isso a distinção entre elas é fundamental para o planejamento terapêutico. **Objetivo:** Através da pergunta formulada: "Qual é a eficácia da dermatoscopia no diagnóstico de lentigo maligno e de lentigo maligno melanoma?", avaliar se a dermatoscopia é um método diagnóstico de boa acurácia para a diferenciação entre Lentigo Maligno e Lentigo Maligno Melanoma. **Métodos:** Realizou-se uma revisão sistemática com metanálise da literatura de estudos nas bases de dados Cochrane collaboration, MEDLINE, PMC, NIH, EMBASE e SCISEARCH que avaliaram comparativamente dermatoscopia e histopatologia do Lentigo Maligno e Lentigo Maligno Melanoma. Utilizamos os descritores: dermatoscopia, lentigo maligno, lentigo maligno melanoma. A seleção dos estudos foi feita através da ferramenta QUADAS-2. **Resultados:** No período de 1996 a 2018, foram encontrados 224 artigos, dos quais 14 foram incluídos para a análise qualitativa e 5 para meta-análise. O teste de Heterogeneidade (*I-square*) para a sensibilidade foi de 97,3% e para a especificidade de 92,8%, mostrando muita heterogeneidade agrupada dos estudos. A sensibilidade agrupada foi de 0,74 (Intervalo de confiança - IC95%: 0,69-0,78) e a especificidade agrupada de 0,78 (IC95%: 0,74-0,82), porém devido à grande inconsistência calculada não confere significância estatística. A Área Sob a Curva foi de 0,9082, mostrando boa acurácia para a dermatoscopia como teste diagnóstico quando comparado à histologia. Estruturas romboidais foi o critério dermatoscópico mais frequente associado à LM/LMM. **Limitações:** Os estudos não avaliaram separadamente LM de LMM. **Conclusão:** Embora a dermatoscopia tenha boa acurácia no diagnóstico de lesões lentiginosas, mais estudos são necessários para determinar se a dermatoscopia é capaz de diferenciar LM de LMM.

Palavras-chave: lentigo maligno, melanoma dermatoscopia**,** diagnóstico, diagnóstico diferencial, revisão sistemática, histopatologia, metanálise.

SUMÁRIO CÁPSULA

• A identificação de estruturas romboidais, pseudorede e áreas homogêneas favorece o diagnóstico de lentigo maligno e lentigo maligno melanoma.

• Demonstramos que há uma falta de estudos sobre o diagnóstico dermatoscópico entre as duas entidades, inviabilizando seu diagnóstico diferencial, mostrando que a histopatologia ainda é necessária para o diagnóstico.

INTRODUÇÃO

O lentigo maligno melanoma (LMM) corresponde à 10% dos melanomas malignos, e recebe essa denominação quando o lentigo maligno (LM) adquire um caráter invasivo vertical.[1] O LM é considerado um melanoma "*in situ*" e em sua evolução de melanócitos atípicos que invadem a derme, caracteriza então o LMM. O LM ocorre em pele cronicamente danificada pelo sol de pacientes acima dos 40 anos, tem crescimento lento e uma taxa de progressão maligna em torno de 5-20% do total.[2]

O padrão-ouro para o diagnóstico de LM e LMM deve ser feito por meio de biópsia mediante características histopatológicas distintas. Estas incluem uma aparência pagetóide de melanócitos, atipia dos melanócitos, pigmentação / distribuição não uniforme dos melanócitos e aumento da densidade dos melanócitos em um fundo de extenso fotodano.[2]

A dermatoscopia é um exame de baixo custo e está à mão do dermatologista como a técnica mais útil para o estudo de lesões melanocíticas da pele para diferenciar as lesões benignas das malignas. É o exame com melhor custo/benefício capaz de direcionar o médico ao melhor sitio para a biópsia. Pode também ser bastante útil na demarcação dos limites de lesões, incluindo os LM/LMM, e no acompanhamento e controle de cura dessas lesões.[1]

A importância de se estabelecer critérios dermatoscópicos para o diagnóstico e diferenciação dessas duas doenças visa a indicação correta do tratamento, visando minimizar os danos de procedimentos invasivos, diminuindo, assim, a morbidade associada e os custos de cirurgias desnecessárias. Em alguns casos a dermatoscopia pode ser um exame barato para a triagem para a realização de outras técnicas diagnósticas não invasivas, como a dermatoscopia confocal, a tomografia de coerência óptica e a ultrassonografia de alta frequência.

No tratamento do LM, terapias conservadoras são descritas, como o uso tópico do imiquimode a 5% e a radioterapia, com taxa de resposta entre 50-100%[4] , enquanto que para o LMM é necessária a excisão cirúrgica com margem de segurança de 0,5-1cm.[5] Deste modo, é importante fazer o diagnóstico diferencial entre as duas lesões, pois com o tratamento conservador geralmente há resultados comésticos muito bons, o que nem sempre é possivel com a cirurgia.

O objetivo deste estudo foi avaliar se a dermatoscopia é um método diagnóstico capaz de realizar o diagnóstico e a diferenciação entre o lentigo maligno e o lentigo maligno melanoma e identificar quais critérios dermatoscópicos têm o potencial de diferenciar lentigo maligno de lentigo maligno melanoma.

MATERIAIS E MÉTODOS

Formulou-se a seguinte pergunta para avaliar o papel da dermatoscopia na diferenciação entre lentigo maligno e lentigo maligno melanoma ao exame dermatológico: Qual é a eficácia da dermatoscopia na diferenciação de lentigo maligno e de lentigo maligno melanoma?

Para abordar a questão, realizou-se pesquisa detalhada e automatizada utilizando os seguintes bancos de dados para a busca dos artigos, sem restrições concernentes à data, ao idioma ou a quaisquer outras variáveis: Cochrane Collaboration; MEDLINE; PMC (PubMed Central) – NIH (*National Institutes of Health*); EMBASE (*The Excerpta Medica Database*); SCISEARCH.

A estratégia de busca dos artigos foi: "Lentigo" OR "Hutchinson's Melanotic Freckle" OR Lentigos OR Lentigines OR Lentiginosis OR Lentiginoses OR (Freckle, Hutchinson's Melanotic) OR (Hutchinson Melanotic Freckle) OR (Hutchinsons Melanotic Freckle) OR (Melanotic Freckle, Hutchinson's) OR (Melanotic Freckle) OR (Lentigo, Malignant) OR (Lentigos, Malignant) OR (Malignant Lentigo) OR (Malignant Lentigos) OR (Freckle, Melanotic) OR (Freckles, Melanotic) OR (Melanotic Freckles) OR (Lentigo Maligna) AND "Dermoscopy" OR Dermoscopies OR Dermatoscopy OR Dermatoscopies OR (Skin Surface Microscopy) OR (Microscopies, Skin Surface) OR (Microscopy, Skin Surface) OR (Skin Surface Microscopies) OR (Surface Microscopies, Skin) OR (Surface Microscopy, Skin) OR (Epiluminescence Microscopy) OR (Epiluminescence Microscopies) OR (Microscopies, Epiluminescence) OR (Microscopy, Epiluminescence) AND "Biopsy" OR Biopsies AND Histopathology.

Três revisores avaliaram independentemente os títulos e os resumos de todos os estudos identificados na busca eletrônica. No caso de discordância, foi feito um consenso. A partir desta ação, foi criada uma coleção de estudos que foram avaliados na íntegra pelos revisores.

Foram selecionados os estudos com grau de recomendação A ou B segundo o documento "Níveis de Evidência 1" da CEBM (*Centre for Evidence-based Medicine*) [6] e foram excluídos os estudos C ou D segundo este mesmo documento.

A avalição dos estudos foi feita através da ferramenta QUADAS (*Quality Assessment of Diagnostic Accuracy Studies*)-2, recomendada para revisões sistemáticas de acurácia diagnóstica pela *Agency for Healthcare Research and Quality, Cochrane Collaboration* e *U.K. National Institute for Health and Clinical Excellence.*[7]

“A ferramenta QUADAS é completada em quatro fases: 1. relatar a pergunta de revisão; 2. desenvolver orientações específicas de revisão; 3. revisar o diagrama de fluxo publicado para o estudo primário ou construir um diagrama de fluxo se nenhum for relatado;

e 4. julgar viés e aplicabilidade, sendo que cada domínio desta fase (Domínio 1 – avaliação da seleção dos pacientes; Domínio 2 – avaliação do teste-índice [dermatoscopia]; Domínio 3 – avaliação do padrão de referência [histopatologia]; e Domínio 4 – avaliação de fluxo e tempo) é avaliado em termos de risco de viés, e os três primeiros domínios também são avaliados em termos de preocupações sobre a aplicabilidade. As perguntas de sinalização foram incluídas para ajudar a julgar o risco de viés; essas questões sinalizam aspectos do desenho do estudo relacionados ao potencial de viés e visam ajudar os revisores a julgar o risco de viés" [7].

Os resultados dos quatro domínios da Fase 4 foram resumidos em uma tabela. A partir desta coleção de estudos foram realizadas as coletas de dados.

Também foram extraídos de cada estudo os critérios dermatoscópicos mais encontrados nas lesões de lentigo maligno / lentigo maligno melanoma.

Definições[8]

- Sensibilidade está relacionada com o potencial de um teste para reconhecer indivíduos com a doença.
- Especificidade representa a probabilidade de resultado de teste negativo em um indivíduo sem a doença.
- Razão de verossimilhança (RV) é definida como a razão do resultado esperado do teste em indivíduos com um determinado estado / doença para os indivíduos sem a doença.
- Razão de verossimilhança para resultados de testes positivos indica qual a probabilidade do resultado positivo do teste ocorrer em indivíduos com a doença em comparação com aqueles sem a doença.
- Razão de verossimilhança para o resultado do teste negativo representa a razão entre a probabilidade de ocorrer um resultado negativo em indivíduos com a doença e a probabilidade de que o mesmo resultado ocorra em indivíduos sem a doença.
- *Odds ratio* diagnóstica (DOR) é uma medida global para precisão diagnóstica, usada para estimativa geral do poder discriminativo de procedimentos diagnósticos e também para a comparação de precisões diagnósticas entre dois ou mais testes diagnósticos. DOR de um teste é a razão entre o grau de positividade em indivíduos com doença em relação à probabilidade em indivíduos sem doença.

Meta-análise

A heterogeneidade entre os estudos incluídos foi avaliada usando o teste *Q* para a significância estatística e a medida de Inconsistência (*I-square*) para quantificar

heterogeneidade, sendo que p <0,1 é estatisticamente significativo e *I-square* > 25% mostra heterogeneidade importante.

Os correspondentes intervalos de confiança (IC) de 95% também foram estimados.

A curva ROC (*receiver operating characteristic*) foi feita para resumir os resultados dos estudos. A área sob a curva (AUC), que resume o desempenho de diagnóstico, foi calculada. Um teste perfeito tem uma AUC próxima a 1 e testes pobres têm AUCs próximos a 0,5. O índice Q*, definido pelo ponto onde a sensibilidade e a especificidade são iguais, que é o ponto mais próximo do ideal no canto superior esquerdo da curva ROC (especificidade= 0, sensibilidade = 1), e os erros padrão de AUC [SE (AUC)] e Q * [SE (Q *)] também foram calculados.

Todos os testes estatísticos foram realizados com um nível de significância de 5%, utilizando-se o software Meta-Disc.[9]

RESULTADOS

Nas bases de dados pesquisadas para o período de 1996 a 2018, foram encontrados 224 artigos, dos quais 14 foram incluídos para a análise qualitativa, num total de 1806 lesões avaliadas.

A Figura 1 mostra a estratégia de pesquisa dos artigos baseados nas instruções do PRISMA.[10] A Tabela I mostra a qualidade dos estudos incluídos, segundo a ferramenta QUADAS-2 e a Tabela II resume as características de cada estudo.

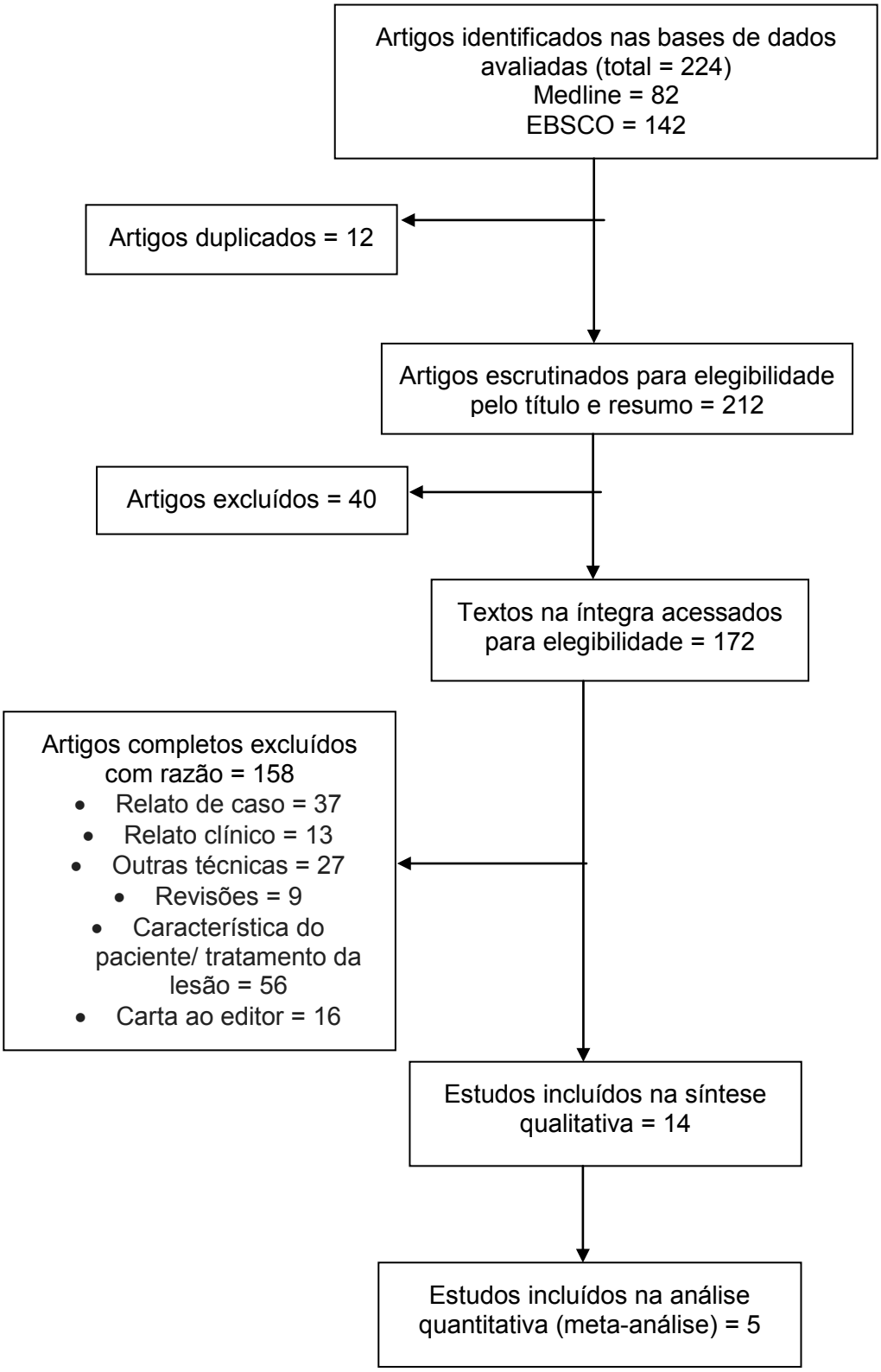

Figura 1 – Estratégia de busca.

Tabela I – Acesso à qualidade dos estudos incluídos.

Estudo		Risco de viés				Aplicabilidade		
Nº	**Autor / ano**	**Seleção dos pacientes**	**Teste-índice**	**Padrão de referência**	**Fluxo e tempo**	**Seleção dos pacientes**	**Teste-índice**	**Padrão de referência**
1	Lallas et al, 2015[11]	BR	BR	BR	BR	BR	BR	BR
2	Jaimes et al, 2015[12]	BR	BR	BR	BR	BR	BR	BR
3	Gomez-Martim et al, 2016[13]	BR	BR	BR	BR	BR	BR	BR
4	Tschandl et al, 2014[14]	BR	IC	IC	BR	BR	AR	IC
5	Pralong et al, 2012[15]	BR	BR	BR	BR	BR	BR	BR
6	Neittaanmaki-Perttu et al, 2015[16]	IC	AR	BR	BR	AR	IC	BR
7	Guitera et al, 2013[17]	BR	AR	IC	BR	BR	BR	IC
8	Goncharova et al, 2013[18]	BR	BR	BR	BR	BR	BR	BR
9	Sahin et al, 2004[19]	BR	BR	BR	BR	BR	BR	BR
10	Ciudad-Blanco et al, 2014[20]	BR	BR	BR	BR	BR	BR	BR
11	Anessi et al, 2016[21]	BR	BR	BR	AR	BR	BR	BR
12	Akay et al, 2010[22]	BR	BR	BR	BR	BR	BR	BR
13	Schiffner et al, 2000[23]	BR	AR	IC	BR	BR	BR	BR
14	Guitera et al, 2010[24]	BR	BR	BR	BR	BR	BR	BR

BR: baixo risco; AR: alto risco; IC: risco incerto. Teste-índice: dermatoscopia. Padrão de referência: histopatologia.

Tabela II – Dados gerais dos estudos.

Nº	Autor / ano	Fonte	Tipo de estudo	Teste usado	Total de casos
1	Lallas et al, 2015[11]	Medline	Retrospectivo	dermatoscopia	144
2	Jaimes et al, 2015[12]	Medline	Prospectivo	dermatoscopia	218
3	Gomez-Martín et al, 2017[13]	Medline	Prospectivo	dermatoscopia microscopia confocal imunoistoquímica	63
4	Tschandl et al, 2014[14]	Medline	Prospectivo	dermatoscopia	240
5	Pralong et al, 2012[15]	Medline	Retrospectivo	dermatoscopia	125
6	Neittaanmaki-Perttu et al, 2015[16]	Medline	Prospectivo	dermatoscopia sistema de imagem espectral	19
7	Guitera et al, 2013[17]	Medline	Prospectivo	dermatoscopia	37
8	Goncharova et al, 2013[18]	Medline	Retrospectivo	dermatoscopia	64
9	Sahin et al, 2004[19]	Medline	Retrospectivo	dermatoscopia	66
10	Ciudad-Blanco et al, 2014[20]	Medline	Retrospectivo	dermatoscopia	200
11	Anessi et al, 2016[21]	Medline	Prospectivo	dermatoscopia	176
12	Akay et al, 2010[22]	Medline	Prospectivo	dermatoscopia	89
13	Schiffner et al, 2000[23]	Medline	Prospectivo	dermatoscopia	87
14	Guitera et al, 2010[24]	Medline	Retrospectivo	dermatoscopia microscopia confocal	210

Os 14 estudos incluídos que compararam a dermatoscopia e a histopatologia não fizeram diferenciação entre lentigo maligno e lentigo maligno melanoma, por isso a análise foi relativa à sensibilidade da dermatoscopia no diagnóstico de ambas as lesões sem

distinção. Destes, de cinco estudos foi possível extrair dados relativos à especificidade e sensibilidade da dermatoscopia.

Foi utilizado o modelo de efeitos aleatório para a combinação de especificidade e sensibilidade. A estatística Q de Cochran para a heterogeneidade mostrou que existe heterogeneidade entre os estudos, tanto para os de especificidade (p = 0,000) quanto para os de sensibilidade (p = 0,000) e que a heterogeneidade é grande para a especificidade (*I-square* - I^2 = 92,8%) e também para a sensibilidade (I^2 = 97,3%). A sensibilidade agrupada foi de 0,74 (IC95%: 0,69-0,78) e a especificidade agrupada foi de 0,78 (IC95%: 0,74-0,82) (Figura 2). O *I-square* para a Razão de verossimilhança positiva foi de 83,7%, para a Razão de verossimilhança negativa foi de 96,1% e para *I-square* para *Odds ratio* diagnóstico foi de 90,4%. A Razão de verossimilhança positiva agrupada foi de 3,68 (IC95%: 2,21-6,13), a Razão de verossimilhança negativa agrupada foi de 0,21 (IC95%: 0,07-0,60) (Figura 3) e para *Odds ratio* diagnóstico grupado foi de 28,20 (IC95%: 4,74-179,23) (Figura 4).

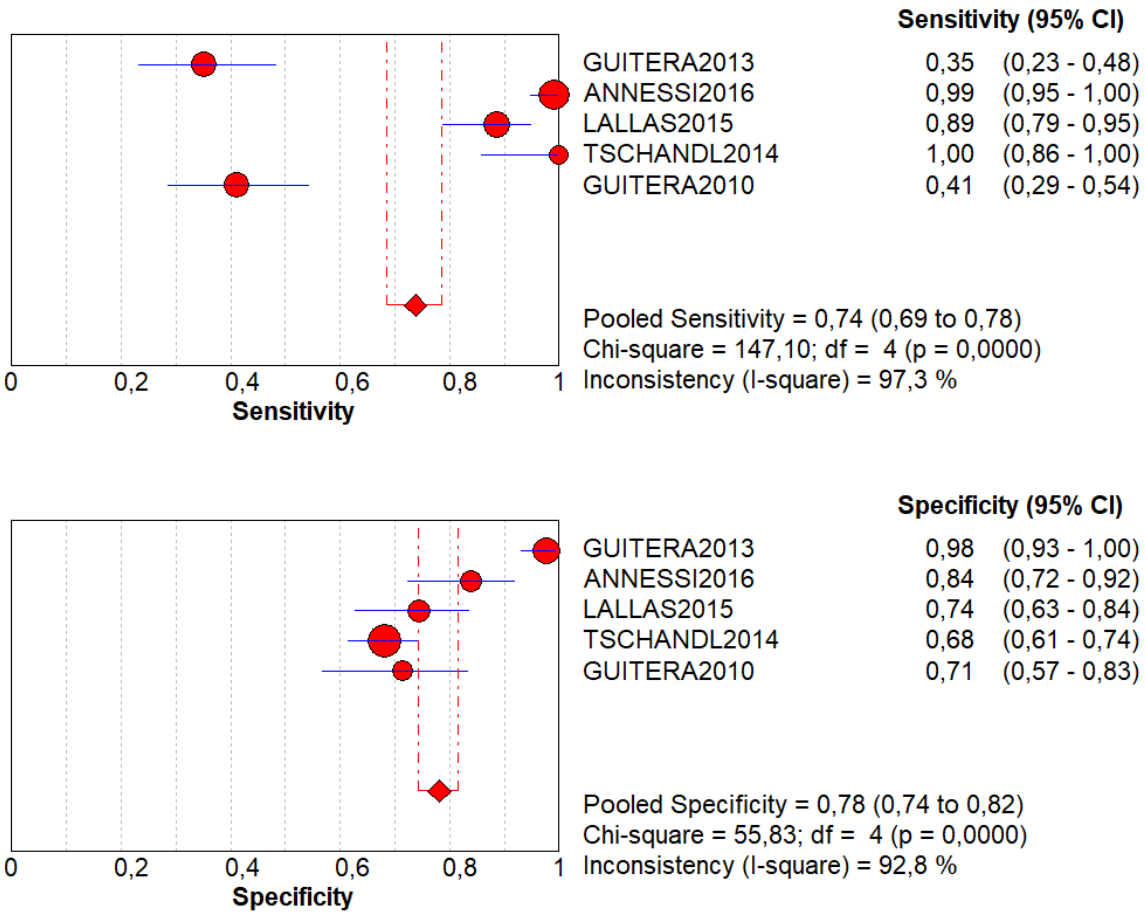

Figura 2 - Diagrama da meta-análise para sensibilidade e especificidade da dermatoscopia.

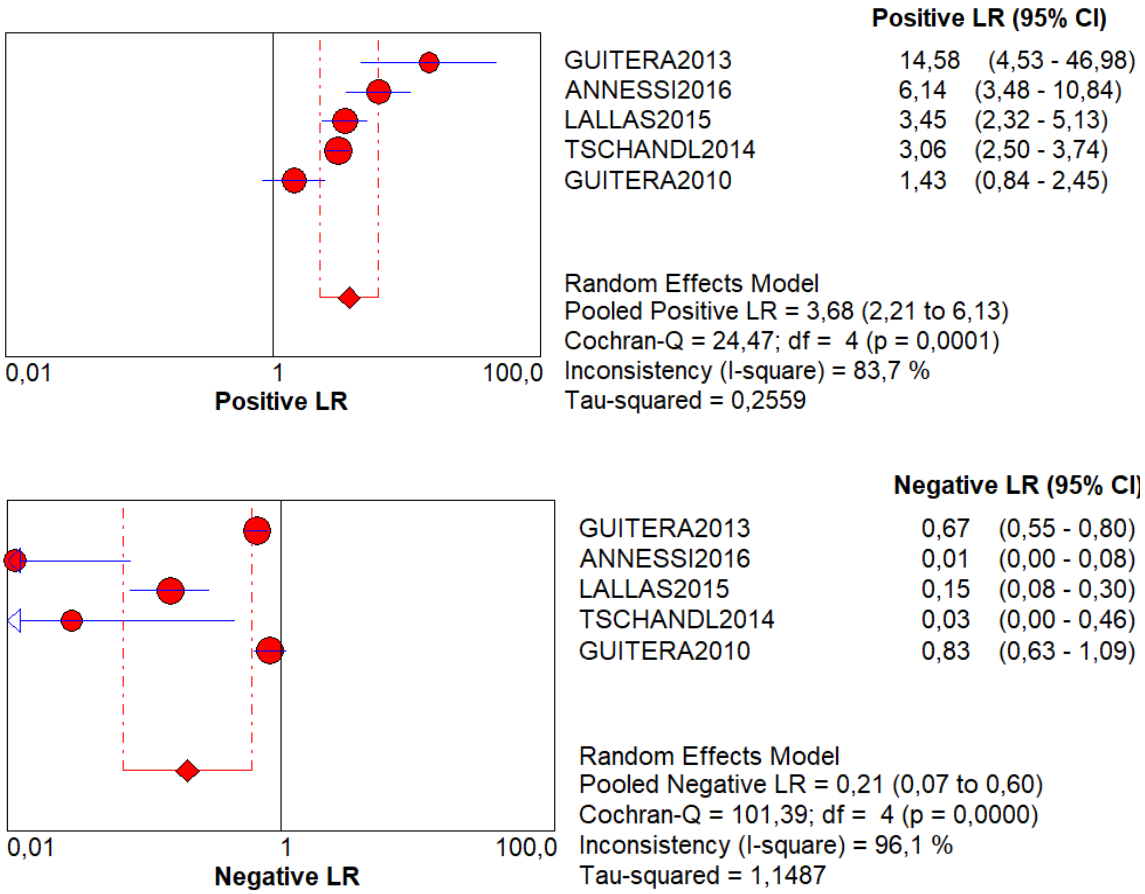

Figura 3 – Diagrama da meta-análise para Razão de verossimilhança positiva e negativa da dermatoscopia.

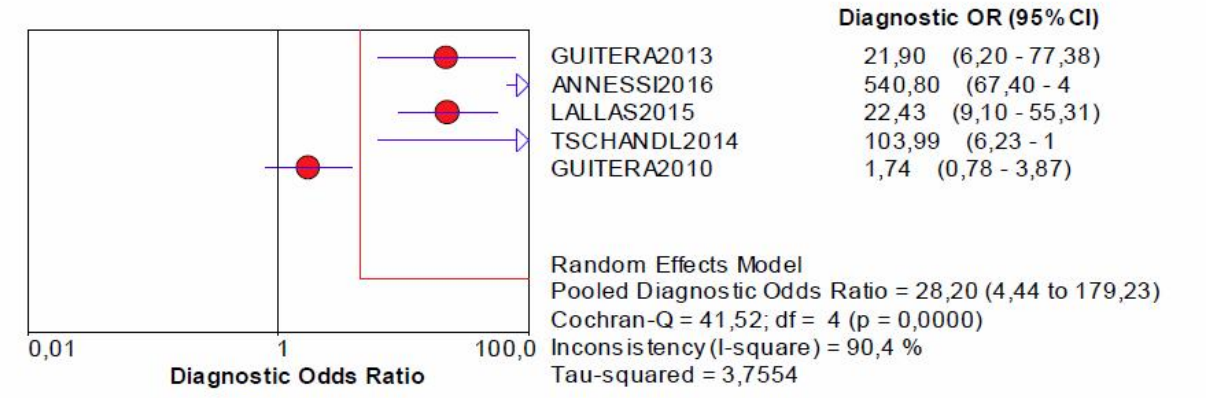

Figura 4 - Diagrama da meta-análise para Odds ratio diagnóstico da dermatoscopia.

A acurácia do teste, medida pela área sob a curva (AUC) foi de 0,908 (SE = 0,0553) (Figura 5).

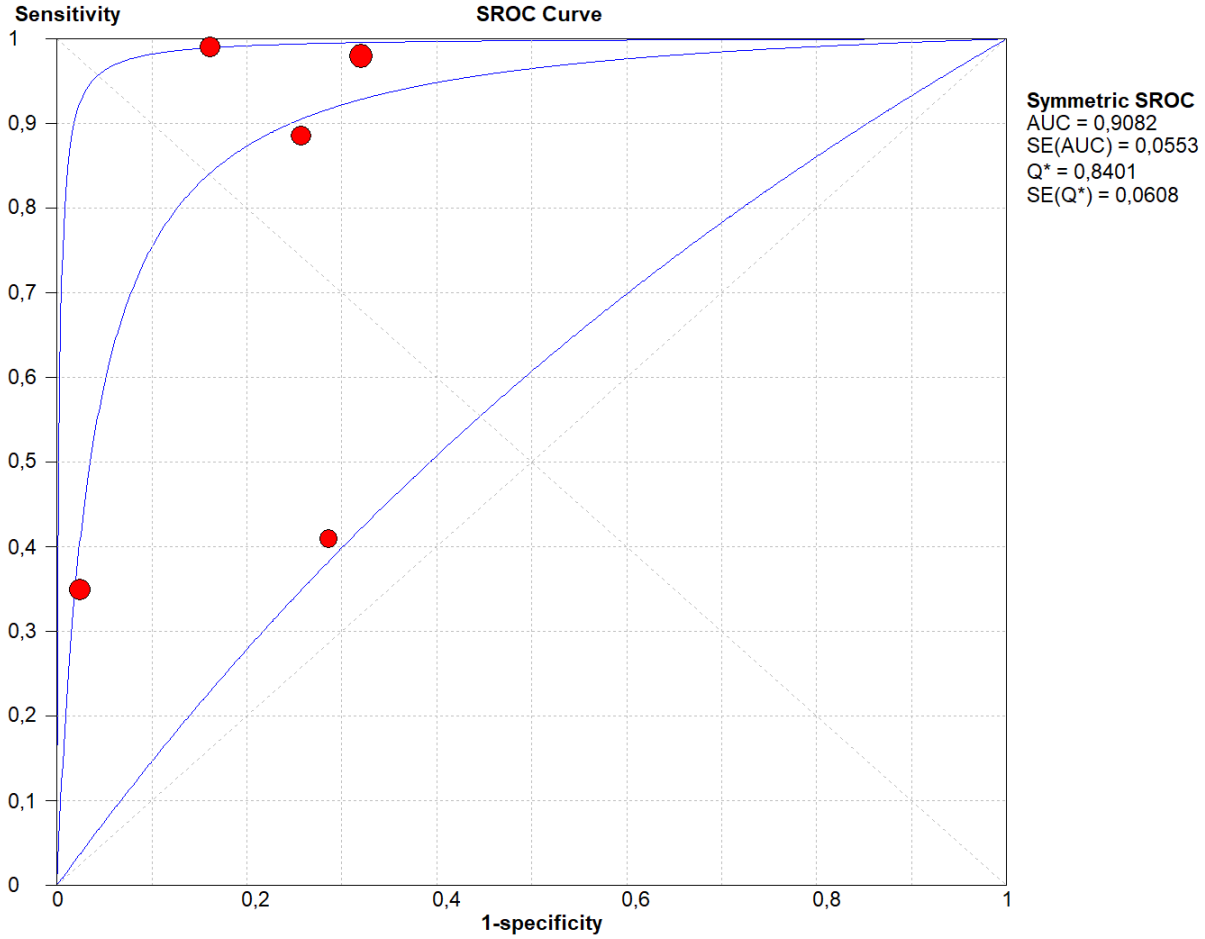

Figura 5 - Curva SROC estimada e os pontos dos dados originais para a dermatoscopia comparada com a histopatologia.

Critérios dermatoscópicos

Foi possível extrair a incidência dos critérios dermatoscópicos utilizados para o diagnóstico de lentigo maligno de onze dos estudos incluídos. Os critérios mais encontrados em cada estudo estão descritos na Tabela III.

Tabela III – Critérios dermatoscópicos que ocorreram em 50% ou mais das lesões de LM/LMM em onze estudos selecionados.

Autor / ano (nº total de casos de LM / LMM no estudo)	**Critério dermatoscópico**	**Nº de casos de LM/LMM que apresentaram o critério (%)**	
Lallas et al, 2015[11] (70)*	Cor Cinza	63 (90)	
	Cor Marrom	63 (90)	
	Círculos Cinza	39 (56)	
	Linhas romboidais cinzas	39 (56)	
		LM	LMM
Jaimes et al, 2015[12] (218 – 142 LM e 76 LMM)[ɣ]	Granulação ou *peppering*	98(69)	25(64,1)
	Cor marrom claro	137(96,5)	38(97,4)
	Cor marrom escuro	130(91,5)	36(92,3)
	Cinza azulado	94(66,2)	31(79,5)
	Azul esbranquiçado	42(29,6)	21(53,8)
	Vasos em ponto	--	22(56,4)
	Blush vascular	--	21(53,8)
	Cor rosa	--	26(66,7)
	Cor branca	--	22(56,4)
Gomez-Martim et al, 2017[13] (24 - 17 LM e 7 LMM)[#]	Aberturas foliculares assimétricas e pigmentadas	16 (67)	
	Pseudonetwork	18 (75)	
	Estruturas romboidais pigmentadas	18 (75)	
Tschandl et al, 2014[14] (24)*	Estruturas Cinza	23 (95,8)	
Pralong et al, 2012[15] (125)[§]	3-4 cores	78 (62)	

	Abertura folicular hiperpigmentada	64 (51)
	Abertura folicular pigmentada	86 (69)
	Aumento de densidade de rede vascular	72 (58)
	Pontos e glóbulos	4 (50)
Goncharova et al, 2013[18] (8)*	Pseudorede	7 (87,5)
	Estruturas homogêneas	6 (75)
	Aberturas foliculares assimétricas e pigmentadas	18 (81,8)
	Linhas escuras	16 (72,7)
	Glóbulos escuros	19 (86,3)
Sahin et al, 2004[19] (22 - 14 LM e 8 LMM)#	Glóbulos cinza	12 (54,5)
	Pontos escuros	16 (72,7)
	Estruturas romboidais escuras (preto e marrom)	11 (50)
	Estruturas romboidais claras	14 (63,6)
	Pseudorede escura	18 (81,8)
Ciudad-Blanco et al, 2014[21] (51)§	Pontos e glóbulos azul-acinzentados	31 (60,8)
	Pseudorede marrom clara/escura	105 (100)
	Rede fina pigmentada marrom	76 (72,4)
Anessi et al, 2016[21] (105)*	Rede pigmentada atípica	70 (66,7)
	Pontos azul-acinzentados	88 (83,8)
	Estruturas em fita marrom escuro/azul acinzentado	80 (76,2)
Akay et al, 2010[22] (20 - 17 LM	Estruturas romboidais	15 (75)

e 3 LMM)[#]	Borrões pretos	15 (75)
	Abertura folicular assimétrica pigmentada	25 (67,6)
Schiffner et al, 2000[23] (37 - 17 LM e 20 LMM) [#]	Linhas escuras	19 (51,3)
	Pontos escuros	32 (86,5)
	Pontos cinzas	28 (75,7)
	Glóbulos escuros	35 (94,6)
	Glóbulos cinza	31 (83,8)
	Áreas escuras homogêneas	23 (62,2)

LM: lentigo maligno; LMM: lentigo maligno melanoma; *somente casos de LM; [Y]: avaliação separada de LM e LMM; [#]: avaliação conjunta de LM e LMM; [§]: somente casos de LMM.

Os critérios dermatoscópicos em comum, mais observados em todos os estudos estão descritos na Tabela IV.

Tabela IV – Critérios dermatoscópicos em comum, mais encontrados nas lesões de lentigo maligno/Lentigo maligno melanoma nos estudos selecionados.

Critério dermatoscópico	Nº de estudos que apresentaram o critério*	Variação da porcentagem de casos que apresentaram o critério
Estruturas romboidais	4 [11,13,19,22]	56-75
Pseudorede	3 [13,14,18]	71-87,5
Áreas homogêneas	3 [18,19,23]	54,5-75
Pontos negros	2 [19,22]	86,4-100
Pontos e glóbulos cinza-azulados	2 [19,20]	60,8-95,8
Cor marrom	2 [11,19]	72,7-90
Círculos cinza	2 [11,19]	54,2-56

*sobrescritos: artigos que apresentaram o critério dermatoscópico descrito.

Dois estudos analisaram especificidade, sensibilidade e risco relativo dos principais critérios dermatoscópicos encontrados.[11,14]

No estudo de Tschandl et al., [14] o critério dermatoscópico com maior sensibilidade foi qualquer estrutura cinza (95.8% - Intervalo de confiança - IC: 78.8–99.3%), porém com especificidade de 30.6% (IC: 24.5–37.2%), e aqueles com maior especificidade foram vasos em ponto (98.1% - IC: 95.3–99.5%), mas com sensibilidade de 8.3% (IC: 1.3–27.0%) e círculo num círculo / duplo círculo, com especificidade de 98.1% (IC: 95.3–99.5%) e sensibilidade de 4.2% (IC: 0.7–21.2%).

No estudo de Lallas et al.,[11] os critérios dermatoscópicos que apresentaram maior risco relativo foram folículos não evidentes (6,33 – IC: 3,06-12,98) e círculos cinza (5,9 – IC: 2,76-12,65).

DISCUSSÃO

Em relação à avaliação da qualidade dos 14 trabalhos estudados, apenas três estudos apresentaram incerto/alto risco de viés com relação ao teste índice (dermatoscopia);[14,16,23] a maioria dos trabalhos incluídos tinha um baixo risco de viés com relação ao teste índice e escolha de pacientes e fluxo e tempo. Porém somente um trabalho avaliou em separado LM de LMM[12], assim optou-se por fazer uma análise dos critérios dermatoscópicos para lesões lentiginosas (LM/LMM). Apenas cinco estudos[11,14,17,21,24] apresentavam avaliação de sensibilidade e especificidade para a dermatoscopia no diagnóstico de LM e LMM e somente dois[11,14] avaliaram sensibilidade e especificidade dos critérios dermatoscópicos. Estruturas romboidais foi o critério dermatoscópico mais observado em LM/LMM nos estudos. Dos trabalhos incluídos, três[13,16,24] apresentavam ao menos outro método diagnóstico, sendo o mais prevalente a dermatoscopia confocal.

A eficácia do uso da dermatoscopia é subjetiva, pois depende do profissional realizador do procedimento, pois os critérios utilizados para o diagnóstico variam entre os diversos autores, bem como a interpretação desses critérios durante o exame. Por isso estudos que descreveram a análise dermatoscópica, sem revisão por outro dermatologista, foram considerados com risco de viés incerto/alto com relação ao teste índice (dermatoscopia).

As informações de revisões sistemáticas de testes de diagnóstico são importantes para a determinação da utilização adequada e eficaz de testes de diagnóstico na prática clínica, e também para o desenvolvimento de informações necessárias para direcionar pesquisas futuras em medicina diagnóstica.[25]

Nos estudos incluídos, observamos que apenas um faz a diferenciação entre os critérios dermatoscópicos de LM e LMM[15], sugerindo existir uma tendência a estudar tais doenças como sendo a mesma entidade, ou talvez a dificuldade de diferenciação dermatoscópica de ambas as lesões através dos critérios existentes.

Nos cinco estudos[11,14,17,21,24] que descreveram a sensibilidade e a especificidade do teste, a dermatoscopia para LM/LMM mostrou sensibilidade agrupada de 0,74 e especificidade agrupada de 0,78. A RV positiva agrupada foi de 3,68, a RV negativa de 0,21 e a DOR agrupada de 28,20. Bons testes diagnósticos apresentam RV positiva maior que 10 e RV negativa menor que 0,1.[8] Estes quatro dados (sensibilidade e especificidade agrupadas, RV positiva e negativa agrupadas e DOR agrupada) mostram que a dermatoscopia não é um teste de excelência para o diagnóstico de lesões lentiginosas. Porém, testes diagnósticos com AUC entre 0,9-1,0 tem uma excelente acurácia diagnóstica[8], e em nosso estudo a AUC foi de 0,9082. Este ocorrido pode ser justificado pelo fato de que os estudos apresentam algumas limitações gerais em seu desenho, como, heterogeneidade das lesões avaliadas, avaliação indistinta entre LM e LMM, pequena

número de casos avaliados, estudos retrospectivos e grande heterogeneidade de especificidade e sensibilidade entre os estudos. Por isso, é importante fazer uma análise crítica dos resultados de sensibilidade e especificidade da dermatoscopia para o diagnóstico de lesões lentiginosas.

Atualmente existem critérios clássicos utilizados na dermatoscopia, porém nota-se que diversos autores tentam elucidar o diagnóstico dessas lesões aprimorando critérios padronizados pré-existentes [26] e por vezes introduzindo novos critérios do LM e LMM, como Pralong et al. [15] que introduzem 4 novos critérios (escurecimento ao exame dermatoscópico, padrão alvo-símile, estruturas romboidais vermelhas e aumento da densidade da rede vascular) ou Tschandl et al.[14] ("four-dot clods", círculo duplo, círculos incompletos e "borda em mordedura").

Na avaliação dos critérios dermatoscópicos, que foram identificados em mais de 50% das lesões biopsiadas de LM/LMM, estruturas romboidais foi o critério dermatoscópico que apareceu em mais estudos (quatro), com incidência variando entre 56 a 75% dos casos, seguido por Pseudorede (incidência entre 71-87,5% dos casos) e áreas homogêneas (incidência entre 54,5 a 75% dos casos), identificados em três artigos. Assim, sugerimos que, a identificação destes critérios à dermatoscopia favoreça o diagnóstico de LM/LMM.

Embora, qualquer estrutura cinza tenha sido o critério dermatoscópico mais sensível e vasos em ponto e círculo num círculo / duplo círculo, os mais específicos, a especificidade e a sensibilidade dos critérios dermatoscópicos só foi avaliada em dois artigos,[11,14] com pequeno número de casos estudados e apenas avaliação de LM, não permitindo uma extrapolação adequada destes achados para todas as lesões lentiginosas.

Esta revisão sistemática oferece evidência para os critérios previamente utilizados no diagnóstico dermatoscópico do LM e do LMM, como os descrito por Stolz et al. [26] (abertura folicular hiperpigmentada, padrão anular-granular, estruturas romboidais pigmentadas e folículos pilosos obliterados), bem como para novos critérios utilizados pelos autores que podem ser considerados na avaliação dessas lesões pela prevalência de aparecimento nos trabalhos, como é o caso de áreas homogêneas, pontos negros, pontos e glóbulos cinza-azulados, cor marrom e círculo cinza. Podemos, então, sugerir aqui que estes critérios sejam incorporados aos critérios clássicos usualmente pesquisados, talvez até mesmo criando uma nova classificação diagnóstica (ou nomenclatura).

CONCLUSÃO

Embora a dermatoscopia pareça ter uma boa acurácia para o diagnóstico de Lentigo Maligno e Lentigo Maligno Melanoma, mais estudos comparando dermatoscopia e histopatologia são necessários para determinar se há critérios dermatoscópicos que possam diferenciar as duas lesões.

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Anexos

ANEXOS

Anexo A - Aprovação do Trabalho pelo Comitê Assessor de Pesquisa Institucional (CAPI) da Universidade do Oeste Paulista - UNOESTE.

12/05/2017 Certificado

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Declaramos para os devidos fins que o Projeto de Pesquisa intitulado **"DERMATOSCOPIA: UMA TÉCNICA APLICÁVEL PARA A DIFERENCIAÇÃO ENTRE LENTIGO MALIGNO E LENTIGO MALIGNO MELANOMA? UM ESTUDO POR METANÁLISE"**, cadastrado na Coordenadoria de Pesquisa, Desenvolvimento e Inovação (CPDI) sob o número nº **3712** e tendo como participante(s) **MURILO DE OLIVEIRA LIMA CARAPEBA (discente), MARIANA ALVES PINEZE (discente), GISELE ALBORGHETTI NAI (orientador responsável)**, foi avaliado e **APROVADO** pelo **COMITÊ ASSESSOR DE PESQUISA INSTITUCIONAL (CAPI)** da Universidade do Oeste Paulista - UNOESTE de Presidente Prudente/SP.

Presidente Prudente, 12 de Maio de 2017.

Prof. Dr. Jair Rodrigues Garcia Jr.
Coordenador Científico da CPDI

Anexo B – Normas de publicação da revista científica a qual o artigo será submetido.

JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

The Official Publication of the American Academy of Dermatology

AUTHOR INFORMATION PACK

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DESCRIPTION

The Journal of the American Academy of Dermatology (JAAD), the official scientific publication of the American Academy of Dermatology (AAD), aims to satisfy the educational needs of the dermatology community. As the specialty's leading journal, JAAD features original, peer-reviewed articles emphasizing: clinical, investigative, and population-based studies healthcare delivery and quality of care research high quality, cost effective, and innovative treatments new diagnostic techniques, and other topics related to the prevention, diagnosis, and treatment of disorders of the skin, hair, and nails Each issue includes continuing medical education articles designed to fill practice and knowledge gaps in the delivery of dermatologic care. JAAD is also the official venue for practice guidelines established by the AAD. Our ultimate goal is to provide readers with content that advances the breadth and depth of dermatologic expertise by disseminating evidence-based recommendations to improve patient outcomes.

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