

ORIGINAL RESEARCH

Is dermoscopy a good tool for the diagnosis of lentigo maligna and lentigo maligna melanoma? A meta-analysis

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Introduction: Dermoscopy is a low-cost examination performed by a dermatologist and good for the diagnosis of pigmented lesions. However, dermoscopy diagnosis of lentigo maligna (LM) and lentigo maligna melanoma (LMM) is still questionable. The objective of this study was to evaluate whether dermoscopy is an effective diagnostic method to diagnose LM/LMM from other pigmented skin lesions, and to identify which are the most frequent dermoscopic criteria associated with LM/LMM

Methods: For this systematic review and meta-analysis, we used the following descriptors: dermoscopy, lentigo maligna, lentigo maligna melanoma, histopathology; and the following databases to search for articles: Cochrane Collaboration, MEDLINE; PMC (PubMed Central) -NIH (National Institutes of Health), EMBASE (The Excerpt Medical Database), and SCISEARCH, from inception to March 30, 2018. The evaluation of studies was performed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool. The PRISMA (Preferred Reporting Itens for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines were followed for data extraction. Also, we extracted from each study the dermoscopic criteria most commonly found in the lesions of LM/LMM.

Results: This systematic review included 15 articles for qualitative analysis (a total of 2,012 lesions evaluated) and 7 for meta-analysis. In the bivariate model the mean sensitivity was 0.824 and the mean specificity was 0.835. The area under the curve was 0.889. Rhomboid structures, pseudonetwork, and homogeneous areas were the most frequent dermoscopic criteria associated with LM/LMM.

Conclusion: These findings suggest that dermoscopy has good accuracy in the diagnosis of LM/

Keywords: melanoma, diagnosis, systematic review, histopathology, biopsy

Introduction

Lentigo maligna melanoma (LMM) accounts for 10% of the malignant melanomas and describes when lentigo maligna (LM) acquires a vertical invasive phase. LM is considered an in situ melanoma, and in its evolution of atypical melanocytes that invade the dermis, it is characterized as LMM. LM occurs in chronically sun-damaged skin, has slow growth, prevalent in patients aged over 40 years and has a malignant progression rate of approximately 5–20% of the total.²

The gold standard for the diagnosis of LM and LMM should be made using biopsy with distinct histopathological characteristics. These include a pagetoid appearance of

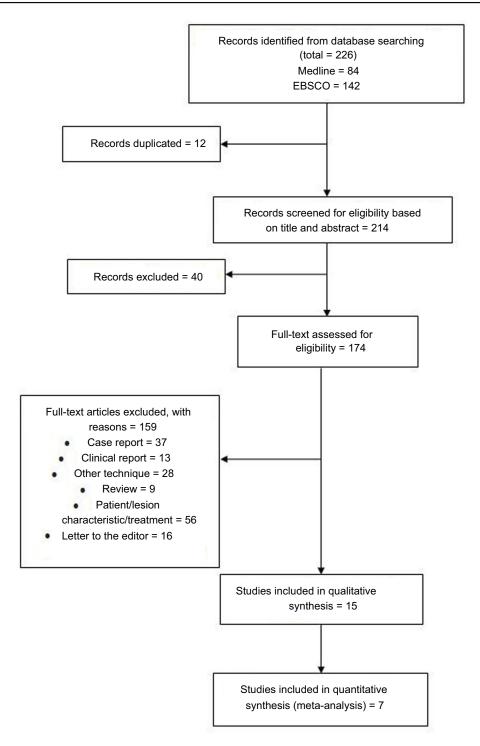


Figure I Search strategy.

melanocytes, melanocyte atypia, nonuniform pigmentation/distribution of melanocytes, and increased melanocyte density in a background of extensive photodamage.²

Dermoscopy is a low-cost examination performed by a dermatologist that is the most useful technique to study melanocytic skin lesions in the differentiation of benign lesions from malignant lesions. It is the most cost-effective examination that can direct the dermatologist to the best site for biopsy. It can also be very useful in the demarcation of lesion limits such as those of LM/LMM and to follow-up and perform cure control of these lesions.¹

The LM/LMM diagnosis based on dermoscopy is ambiguous. For example, asymmetric pigmented follicular openings, hyperpigmentation of the follicle rim, light

brown pseudonetworks, light rhomboidal structures, light streaks, and peripheral gray dots could be observed in actinic keratosis and in LM/LMM.²

The importance of establishing dermoscopic criteria for the diagnosis of LM/LMM is due to the correct selection of treatment, to minimize the damage of invasive procedures and reduce the associated morbidity and costs of unnecessary surgeries. In some cases, dermoscopy may be a cheap screening test for other noninvasive diagnostic techniques, such as confocal dermoscopy, optical coherence tomography, and high-frequency ultrasonography.³

Information from systematic reviews of diagnostic tests is important to determine the appropriate and effective use of diagnostic tests in clinical practice and to develop information necessary to determine the directions of future research in diagnostic medicine.⁴

The aim of this study was to evaluate whether dermoscopy is an effective diagnostic method to differentiate LM and LMM from other pigmented skin lesions and to identify which are the most frequent dermoscopic criteria associated with LM/LMM.

Methods

The following question was asked to evaluate the role of dermoscopy in the diagnosis of lentigo maligna and lentigo maligna melanoma on dermatological examination: What is the efficacy of dermoscopy in the diagnosis of lentigo maligna and lentigo maligna melanoma compared to histopathology?

Data source and search strategy

To address the issue, we conducted detailed and automated research using the following databases to search for articles, without any restrictions regarding the date, language or any other parameter: Cochrane Collaboration; MEDLINE; PMC (PubMed Central) - NIH (National Institutes of Health); EMBASE (The Excerpt Medical Database); SCISEARCH from inception of these databases to March 30, 2018.

The search strategy of the articles was as follows: "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) OR (Melanotic Freckle) OR (Lentigo, Malignant) OR (Lentigos, Malignant) OR (Malignant Lentigos) OR (Freckle, Melanotic) OR (Freckles, Melanotic) OR (Melanotic)

Freckles) OR (Lentigo Maligna) AND "Dermoscopy" OR Dermoscopies OR Dermatoscopies OR (Skin Surface Microscopy) OR (Microscopies, Skin Surface) OR (Microscopy, Skin Surface) OR (Skin Surface Microscopies) OR (Surface Microscopies, Skin) OR Microscopy, Skin) OR (Epiluminescence (Surface Microscopy) OR (Epiluminescence Microscopies) OR (Microscopies, Epiluminescence) OR (Microscopy, Epiluminescence) AND "Biopsy" OR Biopsies AND 'Histopathology'.

Eligibility criteria and study selection

The studies with a grade of recommendation A or B were selected according to the document "Levels of Evidence 1" of the CEBM (Center for Evidence-based Medicine),⁵ and the C or D studies listed in this document were excluded.

Quality assessment of included studies

The evaluation of the studies was performed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool, recommended for systematic reviews of diagnostic accuracy by the Agency for Healthcare Research and Quality, Cochrane Collaboration, and UK National Institute for Health and Clinical Excellence.⁶

Data extraction

Two authors (MOLC and MAP) independently assessed the titles and abstracts of all studies identified in the electronic search. In the event of disagreement, a consensus was reached. From this action, a collection of studies that affirmatively answered our question was created that was evaluated in their entirety by the authors.

From each study were extracted the tests used to evaluate the lesions, which lesions were evaluated and their location and the number of cases evaluated. The general sensitivity and specificity of dermoscopy were extracted for meta-analysis.

Additionally, we extracted from each study the dermoscopic criteria most commonly found in the lesions of LM/LMM.

Definitions

 The definitions for sensitivity, specificity, likelihood ratio (LR), likelihood ratio for a positive test, likelihood ratio for a negative test, and diagnostic odds ratio (DOR) can be found in the article by Šimundić.⁷

Table I General data of the studies

<u>, </u>	Reference/year S	Source	Type of study	Test used	Lesions evaluated	Location of the lesions evaluated	Total number of cases	Sensitivity (%)	Specificity (%)
t al, 2015 ¹³ Medline Retrospective Dermoscopy Martin et al, Medline Prospective Dermoscopy et al, 2012 ¹⁶ Medline Retrospective Dermoscopy et al, 2013 ¹⁷ Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2010 ²² Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁵ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	Pigmented actinic keratosis/LM	Facial lesions	144	68	74
Martin et al, Medline Prospective Dermoscopy I et al, 2014 ¹⁵ Medline Prospective Dermoscopy et al, 2013 ¹⁷ Medline Retrospective Dermoscopy Prospective Dermoscopy Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2010 ²¹ Medline Retrospective Dermoscopy al, 2010 ²² Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy at al, 2010 ²⁴ Medline Retrospective Dermoscopy Reflectance confocal at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal at al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Retrospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	Melanoma/LM	Nonfacial	218	SN	SN
Martín et al, Medline Prospective Dermoscopy I et al, 2012 ¹⁶ Medline Retrospective Dermoscopy et al, 2013 ¹⁷ Medline Retrospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2010 ²² Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁵ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal						lesions			
l et al, 2014 ¹⁵ Medline Prospective Dermoscopy et al, 2013 ¹⁷ Medline Retrospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2010 ²² Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Prospective Dermoscopy et al, 2010 ²⁵ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁵ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal	Martín et al,	1edline	Prospective	Dermoscopy	LM/LMM/benign pigmented lesions	Facial lesions	63	SZ	SN
et al, 2014 ¹⁵ Medline Prospective Dermoscopy et al, 2013 ¹⁷ Medline Retrospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy t al, 2016 ²¹ Medline Retrospective Dermoscopy et al, 2010 ²² Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2017 ²⁵ Medline Retrospective Dermoscopy set al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal t al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Retrospective Dermoscopy Reflectance confocal	4			Immunohistochemistry				SZ	NS
et al, 2012 ¹⁶ Medline Retrospective Dermoscopy et al, 2013 ¹⁷ Medline Prospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy al, 2010 ²² Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy at al, 2010 ²⁵ Medline Retrospective Dermoscopy et al, 2010 ²⁶ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal and 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal and 2018 ²⁶ Redline Retrospective Dermoscopy Reflectance confocal		1edline	Prospective	Dermoscopy	LM/basal cell carcinomas/	Facial lesions	240	95.8	89
et al, 2012 ¹⁶ Medline Retrospective Dermoscopy ova et al, Medline Retrospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy t al, 2016 ²¹ Medline Prospective Dermoscopy et al, 2010 ²² Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2017 ²⁵ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal et al, 2017 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Retrospective Dermoscopy Reflectance confocal Reflectance confocal					pigmented actinic keratoses				
et al, 2013 ¹⁷ Medline Prospective Dermoscopy ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy t al, 2010 ²² Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal t al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal t al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	LMM/benign pigmented lesions	Facial lesions	125	SZ	SN
ova et al, Medline Retrospective Dermoscopy al, 2004 ¹⁹ Medline Retrospective Dermoscopy t al, 2016 ²¹ Medline Prospective Dermoscopy et al, 2010 ²² Medline Prospective Dermoscopy et al, 2000 ²⁴ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal		1edline	Prospective	Dermoscopy	LM/LMM/benign pigmented lesions	Facial lesions	37	35	86
al, 2004 ¹⁹ Medline Retrospective Dermoscopy lanco et al, Medline Retrospective Dermoscopy t al, 2016 ²¹ Medline Prospective Dermoscopy et al, 2000 ²³ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy let al, 2017 ²⁵ Medline Retrospective Dermoscopy let al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal	ova et al,	1edline	Retrospective	Dermoscopy	seborrheic keratosis/pigmented actinic keratosis/LM/	Facial lesions	4	SZ	SN
al, 2004 ¹⁹ Medline Retrospective Dermoscopy Blanco et al, Medline Retrospective Dermoscopy al, 2010 ²² Medline Prospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy et al, 2010 ²⁵ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal Retrospective Dermoscopy Reflectance confocal	81				solar lentigo				
Blanco et al, Medline Retrospective Dermoscopy at al, 2016 ²¹ Medline Prospective Dermoscopy r et al, 2000 ²³ Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy Reflectance confocal at al, 2017 ²⁵ Medline Prospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	Lentigo senilis-initial seborrheic keratosis, seborrheic	Facial lesions	99	NS	NS
Blanco et al, Medline Retrospective Dermoscopy at al, 2016 ²¹ Medline Prospective Dermoscopy at al, 2010 ²² Medline Retrospective Dermoscopy et al, 2010 ²⁴ Medline Retrospective Dermoscopy at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal at al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal					keratosis/LM/LMM				
al, 2016 ²¹ Medline Prospective Dermoscopy al, 2010 ²² Medline Prospective Dermoscopy r et al, 2000 ²³ Medline Retrospective Dermoscopy et al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal et al, 2017 ²⁵ Medline Retrospective Dermoscopy Reflectance confocal et al, 2018 ²⁶ Medline Retrospective Dermoscopy Reflectance confocal Reflectance confocal	Blanco et al,	1edline	Retrospective	Dermoscopy	Melanoma/LM	Facial and	200	SZ	SZ
Medline Prospective Dermoscopy Medline Retrospective Dermoscopy Medline Retrospective Dermoscopy Reflectance confocal Medline Prospective Dermoscopy Reflectance confocal	20					nonfacial			
Medline Prospective Dermoscopy Medline Retrospective Dermoscopy Medline Retrospective Dermoscopy Reflectance confocal Medline Prospective Dermoscopy Reflectance confocal						lesions			
Medline Retrospective Dermoscopy Medline Retrospective Dermoscopy Reflectance confocal Medline Prospective Dermoscopy Reflectance confocal		1edline	Prospective	Dermoscopy	Solar lentigo/seborrheic keratosis/LM	Lesions of	176	66	84
Medline Retrospective Dermoscopy Medline Retrospective Dermoscopy Reflectance confocal Medline Prospective Dermoscopy Reflectance confocal						the head			
Medline Retrospective Dermoscopy Retrospective Dermoscopy Reflectance confocal		1edline	Prospective	Dermoscopy	Pigmented actinic keratosis/LM	Facial lesions	68	SZ	SN
Medline Retrospective Dermoscopy Reflectance confocal Medline Prospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	LM/benign pigmented lesions	Facial lesions	87	SZ	SN
Medline Prospective Dermoscopy Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal Reflectance confocal		1edline	Retrospective	Dermoscopy	Benign macules/LM	Facial lesions	210	4	71
Medline Prospective Dermoscopy Reflectance confocal Medline Retrospective Dermoscopy Reflectance confocal				Reflectance confocal				82	93
Reflectance confocal Medline Retrospective Dermoscopy Reflectance confocal		1edline	Prospective	Dermoscopy	Seborrhoeic keratosis/LM/Melanoma/Basal cell	Facial lesions	70	95	84
Medline Retrospective Dermoscopy Reflectance confocal				Reflectance confocal	carcinoma			95	82
		1edline	Retrospective	Dermoscopy	LM/LMM/solar lentigines/Seborrhoeic keratosis/Basal	Facial lesions	223	19	92
				Reflectance confocal	cell carcinoma/pigmented actinic keratosis/nevi/liche-			80	18
noid keratoses/s					noid keratoses/scars/pigmented Bowen's disease				

Abbreviations: LM, lentigo maligna; LMM, lentigo maligna melanoma; NS, not stated.

Meta-analysis

The heterogeneity among the included studies was assessed using the Q test for statistical significance and the I-square test to quantify heterogeneity, where p<0.1 is statistically significant and I-square >25% shows significant heterogeneity. The corresponding 95% confidence intervals (CI) were also estimated.

The receiver operating characteristic (ROC) curve was used to summarize the results of the studies. The area under the curve (AUC), which summarizes the diagnostic performance, was calculated. A perfect test has an AUC close to 1, and poor tests have AUCs close to 0.5. The index Q*, defined by the point where the sensitivity and specificity are equal, is the nearest point of the ideal in the upper left corner of the ROC curve (specificity =0, sensitivity =1), and the standard errors of AUC [SE (AUC)] and Q * [SE (Q *)] were also calculated. The statistical tests were performed using Meta-Disc software.⁸

The bivariate model of Reitsma et al⁹ was used to enhance the understanding of the heterogeneity of results between studies and the correlation within studies. For the bivariate analysis, we used the Software R v. 3.5.3 with the package MADA (Meta-Analysis of Diagnostic Accuracy) v. 0.5.8.

All statistical tests were performed with a significance level of 5%.

Results

In the databases searched for the period from 1996 to 2018, 226 articles were found, from which 15 were included for qualitative analysis among a total of 2,012 lesions evaluated.

Figure 1 shows the search strategy of the articles based on the PRISMA (Preferred Reporting Itens for Systematic Reviews and Meta-Analyses)¹⁰ and MOOSE (Meta-analysis Of Observational Studies in Epidemiology)¹¹ guidelines. Table 1 summarizes the characteristics of each study.

Regarding the quality evaluation of the 15 studies, only 2 studies^{15,23} presented an uncertain/high risk of bias in relation to the index test (dermoscopy); most of the included studies had a low risk of bias with respect to the index test and patient choice and flow and time (Table 2).

Of the 15 included studies comparing dermoscopy and histopathology, from 7 studies, ^{12,15,17,21,24–26} it was possible to extract data on the general specificity and sensitivity of dermoscopy. These seven studies were included in the quantitative analysis (meta-analysis).

The random-effects model was used for the combination of specificity and sensitivity. Cochran's Q statistic for heterogeneity showed the heterogeneity between the studies, both for specificity (p<0.001) and sensitivity (p<0.001), and that heterogeneity is large for specificity [I-square (I²) =91.2%] and for sensitivity (I²=96.3%). The pooled sensitivity was 0.71 (95% CI: 0.67-0.76), and the pooled specificity was 0.81 (95% CI: 0.78-0.84) (Figure 2). The I-square value for the positive likelihood ratio (LR) was 84.1%, that for the negative LR was 94.4% and that for the diagnostic odds ratio (DOR) was 86.9%. The pooled positive LR was 4.352 (95% CI: 2.734-6.925), the pooled negative LR was 0.248 (95% CI: 0.122-0.503), and the pooled DOR was 28.47 (95% CI: 7.859–102.68). The accuracy of the test, as measured by the area under the curve (AUC), was 0.9147 (SE=0.0358) (Figure 3).

In the bivariate model, mean sensitivity was 0.824 (95% CI: 0.531–0.951), mean specificity was 0.835 (95% CI: 0.720–0.909), and mean DOR was 30.400 (95% CI: 6.880–92.400). The AUC was 0.889 and the partial AUC (restricted to observed false-positive results and normalized) was 0.712 (Figure 4).

Dermoscopic criteria

It was possible to extract the incidence of the dermoscopic criteria used for the diagnosis of LM/LMM from eleven included studies. The most frequent criteria in each study are described in Table 3.

The common dermoscopic criteria most observed in all studies were rhomboidal structures, described in four studies ^{12,14,19,22} (56–75% of the cases presented the criteria); pseudonetwork, described in three studies ^{14,15,18} (71–87.5% of the cases presented the criteria); homogeneous areas, described in three studies ^{18,19,23} (54.5–75% of the cases presented the criteria); black points, in two articles ^{19,22} (86.4–100% of the cases); blue-gray dots and globules, in two articles ^{19,22} (60.8–95.8% of the cases); brown color in two articles ^{12,19} (72.7–90% of the cases); and gray circles, in two articles ^{12,19} (54.2–56% of the cases).

Two studies^{12,15} analyzed the specificity, sensitivity, and relative risk of the main dermoscopic criteria found. In the study by Tschandl et al,¹⁵ the most sensitive dermoscopic criteria were any gray structure (95.8% CI: 78.8–99.3%), with a specificity of 30.6% (CI: 24.5–37.2%), dot vessels, with a higher specificity (98.1% CI: 95.3–99.5%) and a sensitivity of 8.3% (CI: 1.3–27.0%), and circle in a circle/double circle, with a specificity of 98.1% (CI: 95.3–99.5%) and sensitivity of 4.2% (CI: 0.7–21.2%). In the study of Lallas

Table 2 Quality assessment of the included studies based on the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool

	Risk of bias				Applicability		
Reference/year	Selection of patients	Test-index	Reference standard	Flow and time	Selection of patients	Test-index	Reference standard
Lallas et al, 2015 ¹²	LR	LR	LR	LR	LR	LR	LR
Jaimes et al, 2015 ¹³	LR	LR	LR	LR	LR	LR	LR
Gomez-Martín et al, 2017 ¹⁴	LR	LR	LR	R	LR	LR	LR
Tschandl et al, 2014 ¹⁵	LR	_D	D	LR	LR	품	D
Pralong et al, 2012 ¹⁶	LR	LR	LR	LR	LR	LR	LR
Guitera et al, 2013 ¹⁷	LR	LR	n	LR	LR	LR	D
Goncharova et al, 2013 ¹⁸	LR	LR	LR	LR	LR	R	LR
Sahin et al, 2004 ¹⁹	LR	LR	LR	LR	LR	LR	LR
Ciudad-Blanco et al, 2014 ²⁰	LR	LR	LR	LR	LR	LR	LR
Anessi et al, 2016 ²¹	LR	LR	LR	壬	LR	R	LR
Akay et al, 2010 ²²	LR	LR	LR	LR	LR	LR	LR
Schiffner et al, 2000 ²³	LR	HR	n	LR	LR	LR	LR
Guitera et al, 2010 ²⁴	LR	LR	LR	LR	LR	R	LR
Wurm et al, 2017 ²⁵	LR	LR	LR	R	LR	R	LR
Cinotti et al, 2018 ²⁶	LR	LR	LR	LR	LR	LR	LR

Notes: Test-index: dermoscopy; reference standard: histopathology. **Abbreviations:** LR, low risk; HR, high risk; U, uncertain.

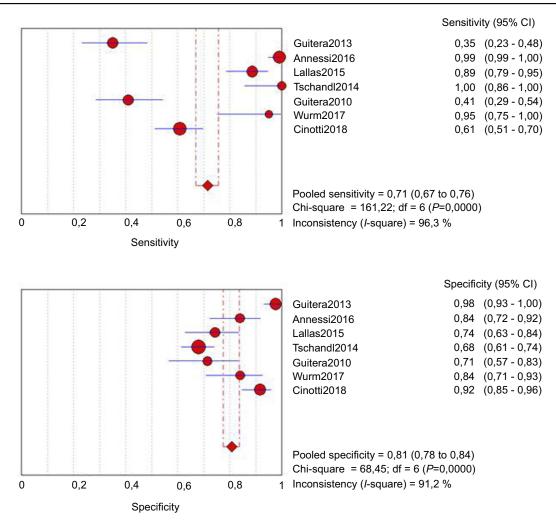


Figure 2 Diagram of the meta-analysis for the sensitivity and specificity of dermoscopy. **Abbreviations:** 95% CI, 95% confidence interval; df, degrees of freedom.

et al,¹² the dermoscopic criteria that presented the highest relative risk were not evident follicles (6.33; CI: 3.06–12.98) and gray circles (5.9; CI: 2.76–12.65).

Discussion

In this meta-analysis, dermoscopy showed a good accuracy in the diagnosis of LM/LMM, demonstrated by AUC between 0.8 and 0.9 in the bivariate model. Also rhomboid structures, followed by pseudonetwork and homogeneous areas were the most observed dermoscopic criteria in LM/LMM in the studies analyzed.

The effectiveness of the use of dermoscopy depends on the professional conducting the procedure because the criteria used for the diagnosis vary among several authors, as well as the interpretation of these criteria during the examination. Therefore, studies that described the dermoscopic analysis without revision by another dermatologist were considered to harbor a risk of uncertain/high bias in relation to the index test (dermoscopy). Only two studies^{15,23} presented an uncertain/high risk of bias in relation to the index test (dermoscopy).

Among the included studies, we observed that only one differentiated between the LMM and LMM dermoscopic criteria, ²³ suggesting a tendency to study such diseases as the same entity or perhaps because of the difficulty of dermoscopic differentiation of both using the existing criteria.

Among the seven studies ^{12,15,17,21,24–26} that described the general sensitivity and specificity, dermoscopy for LM/LMM showed a pooled sensitivity of 0.71 and pooled specificity of 0.81. The pooled positive LR was 4.352, the pooled negative LR was 0.248, and the pooled DOR was 28.407. Good diagnostic tests have positive LRs greater than 10 and negative LRs less than 0.1.⁷ However, diagnostic tests with AUC between 0.9 and 1.0

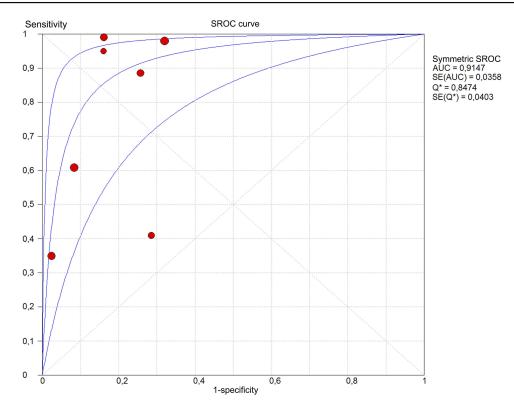


Figure 3 Estimated SROC (Summary Receiver Operating Characteristics) curve and original data points for dermoscopy compared with histopathology. Abbreviations: AUC, area under the curve; SE (AUC), standard errors of AUC; Q*, chi-squared; SE(Q*), standard errors of Q*.

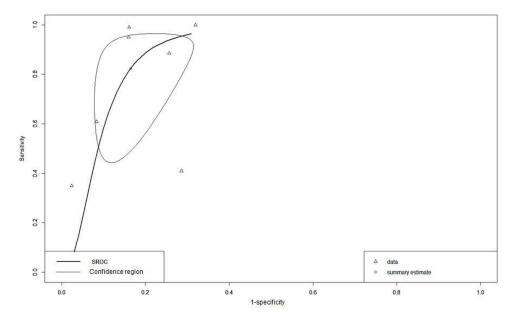


Figure 4 Estimated SROC (Summary Receiver Operating Characteristics) curve (Bivariate model) and the corresponding 95% confidence ellipse.

have excellent diagnostic accuracy;⁷ in our study, the AUC was 0.9147. Although the pooled positive LR and the pooled DOR did not show favorable indices for dermatoscopy, the pooled sensitivity, the pooled specificity, the

pooled negative LR, and AUC favor that dermoscopy is a good test for the diagnosis of LM/LMM.

But the studies included in this meta-analysis present some general limitations in its design, such as the hetero-

Table 3 Dermoscopic criteria occurring in 50% or more of the LM/LMM lesions in eleven selected studies

Reference/year	Dermoscopic criteria	Number of LM/LMM cas criteria (%)	es that presented the
Lallas et al, 2015 ¹²	Gray color	63 (90)	
	Brown color	63 (90)	
	Gray circles	39 (56)	
	Gray rhombic lines	39 (56)	
Jaimes et al, 2015 ¹³		LM	LMM
	Granulation or peppering	98(69)	25(64.1)
	Light brown color	137(96.5)	38(97.4)
	Dark brown color	130(91.5)	36(92.3)
	Bluish gray	94(66.2)	31(79.5)
	Blue whitish	42(29.6)	21(53.8)
	Vases on stitch	-	22(56.4)
	Vascular blush	-	21(53.8)
	Pink color	-	26(66.7)
	White color	-	22(56.4)
Gomez-Martim et al, 2017 ¹⁴	Asymmetric pigmented follicular openings	16 (67)	•
	Pseudonetwork	18 (75)	
	Pigmented rhomboidal structures	18 (75)	
Tschandl et al, 2014 ¹⁵	Gray structures	23 (95.8)	
Pralong et al, 2012 ¹⁶	3–4 colors	78 (62)	
	Hyperpigmented follicular opening	64 (51)	
	Pigmented follicular opening	86 (69)	
	Increased vascular network density	72 (58)	
Goncharova et al, 2013 ¹⁸	Points and globules	4 (50)	
	Pseudonetwork	7 (87.5)	
	Homogeneous structures	6 (75)	
Sahin et al, 2014 ¹⁹	Asymmetrical and pigmented follicular openings	18 (81.8)	
	Dark lines	16 (72.7)	
	Dark globules	19 (86.3)	
	Gray globules	12 (54.5)	
	Dark dots	16 (72.7)	
	Dark rhomboidal structures (black and brown)	11 (50)	
	Clear rhomboidal structures	14 (63.6)	
	Dark pseudonetwork	18 (81.8)	

(Continued)

Table 3 (Continued).

Reference/year	Dermoscopic criteria	Number of LM/LMM cases that presented the criteria (%)
Ciudad-Blanco et al, 2014 ²⁰	Dots and blue-gray globules	31 (60.8)
Anessi et al, 2016 ²¹	Light brown/dark pseudonetwork	105 (100)
	Fine pigmented brown net	76 (72.4)
	Atypical pigmented network	70 (66.7)
	Blue-gray dots	88 (83.8)
	Dark brown/blue-gray ribbon structures	80 (76.2)
Akay et al, 2010 ²²	Rhomboidal structures	15 (75)
	Black blots	15 (75)
Schiffner et al, 2000 ²³	Pigmented asymmetric follicular opening	25 (67.6)
	Dark lines	19 (51.3)
	Dark dots	32 (86.5)
	Gray dots	28 (75.7)
	Dark globules	35 (94.6)
	Gray globules	31 (83.8)
	Homogeneous dark areas	23 (62.2)

Abbreviations: LM, lentigo maligna; LMM, lentigo maligna melanoma.

geneity of lesions evaluated, indistinct evaluation between LM and LMM, a small number of cases evaluated in some studies, retrospective studies, and great heterogeneity of the specificity and sensitivity among the studies included in the meta-analysis. Because of this, we performed a bivariate analysis.

In the bivariate model, that estimates the amount of between-study variability in both sensitivity and specificity and evaluates more adequately studies with a lot of heterogeneity, the mean sensitivity of 0.824, a mean specificity of 0.835, and mean DOR of 30.400. Also, the AUC was 0.889 and the partial AUC was 0.712. Diagnostic tests with AUC between 0.8 and 0.9 have very good diagnostic accuracy and tests with AUC between 0.7 and 0.8 have good diagnostic accuracy. These data show that dermoscopy has a good accuracy for the diagnosis of LM/LMM.

Currently, there are classic criteria used in dermoscopy, but several authors have tried to elucidate the diagnoses of these lesions by improving pre-existing standardized criteria²⁵ and sometimes introducing new criteria, such as

those by Pralong et al,¹⁶ who introduced four new criteria (darkening in dermoscopic examination, target-like pattern, red rhomboidal structures, and increased vascular network density) and Tschandl et al¹⁵ (four-dot clods, double circle, incomplete circles, and edge in bite).

Some authors have described that if asymmetric pigmented follicular openings, dark rhomboidal structures, slate-gray areas, and slate-gray dots/globules/pepper pattern are found in one lesion, they have high sensitivity and specificity for a diagnosis of LMM.^{22,27}

In the assessment of the dermoscopic criteria, which were identified in more than 50% of the biopsied LM/LMM lesions, rhomboidal structures were the dermoscopic criteria that appeared in more studies (four), with an incidence ranging from 56% to 75% of the cases, followed by a pseudonetwork (incidence between 71% and 87.5% of the cases), and homogeneous areas (incidence between 54.5% and 75% of the cases), identified in three articles. Thus, we suggest that the identification of these criteria for dermoscopy favors the diagnosis of LM/LMM.

Although any gray structure was the most sensitive dermoscopic criteria and dot vessels and circle in a circle/double circle were more specific, the specificity and sensitivity of the dermoscopic criteria were only evaluated in two articles, ^{12,15} with a few cases studied that only evaluated LM, preventing adequate extrapolation of these findings to all lentiginous lesions.

This systematic review offers evidence of previously used criteria to diagnose LM and LMM, as described by Stolz et al²⁷ (hyperpigmented follicular opening, annular-granular pattern, pigmented rhomboid structures, and obliterated hair follicles) as well as new criteria used by the authors that can be considered in the evaluation of these lesions by the prevalence of appearance in the studies, such as homogeneous areas, black spots, dots and bluish-gray globules, brown color, and gray circle.

We have to consider that only seven studies ^{12,15,17,21,24–26} presented sensitivity and specificity assessment for dermoscopy in the diagnosis of LM/LMM, and only two ^{12,15} evaluated the sensitivity and specificity of dermoscopic criteria. So, further studies evaluating the sensitivity and specificity of the dermoscopic criteria for LM/LMM may contribute to the improvement of the dermoscopic diagnosis of these lesions.

Conclusion

On the basis of this study, dermoscopy has good accuracy in the diagnosis of LM/LMM compared to histopathology and can be used for define the optimal biopsy site or even for setting the total removal of the lesion. Also the identification of rhomboidal structures, pseudonetwork, and homogeneous areas are the criteria that seem most favor the diagnosis of LM/LMM.

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Disclosure

The authors report no conflicts of interest in this work.

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