Dermatology Practical & Conceptual

The Use of Dermoscopy in the Delineation of Basal Cell Carcinoma for Mohs Micrographic Surgery: a Systematic Review With Meta-Analysis

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ABSTRACT

Introduction: Several studies investigated the use of dermoscopy in the delineation of basal cell carcinoma (BCC) for Mohs micrographic surgery (MMS) with conflicting results.

Objectives: The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods: We included all comparative studies. Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or "standard" MMS.

Results: A total of 6 studies including 508 BCCs were reviewed. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

Conclusions: Dermoscopy allows visualization of structures up to 1mm into the dermis. Therefore, it is rational to use it for lateral margin evaluation. Currently, there are two comparative studies showing the efficacy of dermoscopy for lateral margin evaluation during MMS. Future studies are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.

Introduction

Basal cell carcinoma (BCC) is the most prevalent skin cancer worldwide [1]. The overall incidence has been steadily rising in the last decade throughout the world due to a burgeoning aging population and increased surveillance and diagnosis [2].

The biological behavior of BCC depends on the tumor subtype [1,2]. Undiagnosed and untreated BCC could lead to extensive local destruction and increase both functional and cosmetic morbidity making the treatment and repair approach challenging for the physician.

The National Comprehensive Cancer Network (NCCN) has established guidelines of care for BCCs [3]. High-risk BCCs include recurrent BCC, tumors with ill-defined borders, located on high-risk mask area of the face, arising on sites of prior radiation therapy or harboring aggressive histological features [3]. There are multiple treatment options for BCC such as ablative laser, photodynamic therapy, curettage, cryosurgery, imiquimod, and sonic hedgehog pathway inhibitors [12,2]. However, surgical excision remains the gold standard for treatment of most BCCs [1]. Standard excision is performed with a predefined clinical margin in order to achieve low recurrence rates. Mohs micrographic surgery (MMS) is a specialized surgical technique that combines surgery with pathology. MMS uses horizontal frozen sections to obtain complete margin control resulting in minimal tissue removal with low recurrence rates [1]. MMS proved to be superior to standard excision for high-risk BCC [1]. Slow Mohs is a variant of MMS using formalin-fixed paraffin-embedded sections with similar outcome [4].

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, is a non-invasive imaging technique widely employed for the diagnosis of skin cancers. Some specific dermoscopic patterns are helpful in the diagnosis of BCC [5]. The use of dermoscopy in the demarcation of surgical margins is another scope of its application. For instance, the use of dermoscopy in MMS might help reduce the number of Mohs stages and achieve surgical margin control within the 1st Mohs stage [4,6-11].

Many studies investigated the effectiveness of dermoscopy in tumor delineation for MMS but with varying outcomes [4,6-11]. While some suggested that dermoscopy could help reduce the number of Mohs stages and therefore shorten operative time and cost [4,9,11], others argued against the usefulness of this approach [6,12]. The ambiguity of these findings is further hampered by the lack of randomized studies and systematic reviews.

Objectives

The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods

Search Strategy

This systematic review with meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. We searched the PubMed and Scopus databases from inception up to January 26, 2022 to identify eligible studies. We aimed to identify all relevant studies published in English language. We used the following search algorithm: ("Basal cell carcinoma") AND ("Mohs surgery" or "Slow Mohs" or "micrographic surgery" or "3-D histology" or "microscopically controlled surgery") AND ("dermoscopy" or "dermatoscopy" or "epiluminescence microscopy"). The PubMed and Scopus search strategies are available as supplementary material.

Inclusion and Exclusion Criteria of Studies

Two review authors (NL and FH) independently screened titles and abstracts for eligible studies. Eligible articles were identified on the basis of the following inclusion criteria: (i) comparative studies having at least a group of BCCs treated with dermoscopy-guided MMS, (ii) studies that used a control group of BCCs treated with visual inspection and/or curettage-guided MMS, (iii) articles published in English language. For eligible studies, full articles were retrieved in full and analyzed by two independent authors (NL and FH). Any discrepancy between the two investigators was resolved by consensus.

PICO(S): Populations, Interventions, Comparison, Outcome Measures, Types of Studies

We included all comparative observational as well as randomized clinical trials (RCT). Participants with BCC regardless of the clinical and histological subtype of the tumor were eligible for inclusion.

Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or "standard" MMS. The latter uses visual inspection alone to delineate the tumors. All types of dermoscopy techniques were eligible, regardless of the polarization mode (polarized vs. nonpolarized mode) and the device type (hand-held dermoscopy or video dermoscopy).

The main outcome measure was the proportion of total margin clearance on the first MMS stage. The secondary outcome measures included the: (i) number of Mohs stages required to achieve complete margin control, (ii) the lateral margin involvement rate, and (iii) the recurrence rate.

If one or more outcome measures were missing, we contacted the corresponding author at least twice (with at least one-week interval) to ask whether full data were available. If the contact was unsuccessful, the corresponding article was excluded from the analysis.

Assessment of the risk of bias

Two review authors (NL and FH) independently assessed the quality of consistency and the risk of bias in the eligible studies. Any disagreement was resolved by discussion or by consensus with a third author (CD). MINORS score was used for observational studies [14]. RCT were evaluated using the Jadad score [15] .

Data Synthesis and Statistical Analysis

Results were reported as Odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data (proportion of total margin clearance on the first MMS stage, lateral margin involvement, and recurrence rates) and standardized mean difference with standard error of the mean for continuous data (number of Mohs stages). A random-effects model was used. Forest plots summarized the data. Funnel plot was used to investigate the existence of publication bias. Strategies for addressing heterogeneity included performing a random-effects meta-analysis and subgroup analyses. We performed all calculations using Comprehensive meta-analysis 3.0 package.

We investigated heterogeneity using Cochran Q test. Evaluation of the percentage of variation between the sample estimates was performed using the Higgins I^2 statistic.

Results

Results of the Search

The literature search identified 289 articles (Figure 1). After removing duplicates, 69 articles were screened for eligibility. Fifty-five records were excluded, including not relevant articles (N = 30), papers not published in English (N = 3), editorials and commentary (N = 11), review articles (N = 10) and book chapters (N = 2). Fourteen full-text articles were assessed for eligibility. Among these, 4 were excluded (case reports and noncomparative studies) [16-19]. Three research letters were excluded [11,20,21]. Among these research

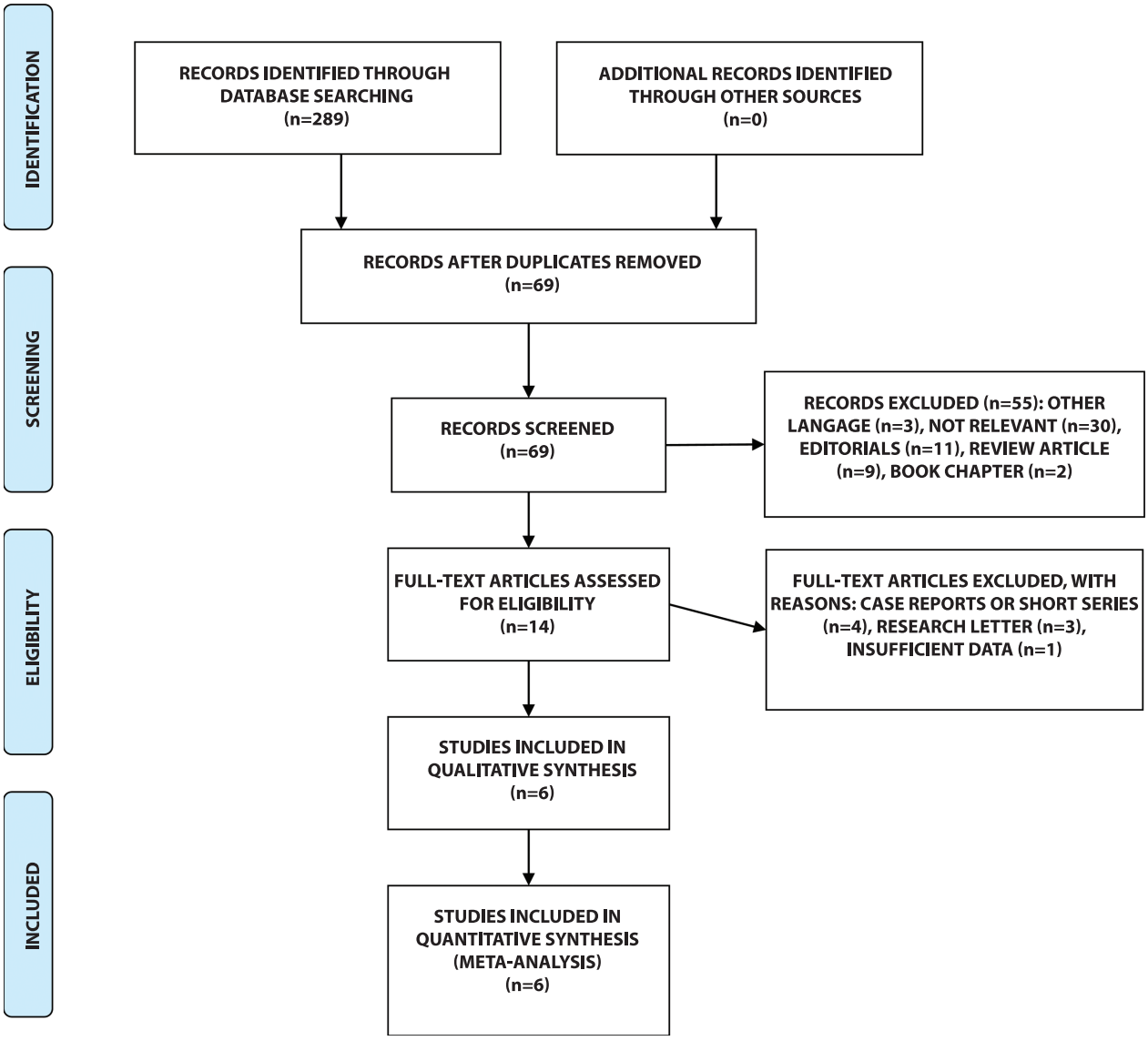


Figure 1. Flow diagram.

letters, two compared dermoscopy to naked eye examination in BCC margin evaluation but the number of Mohs stages in each study group expressed in mean with standard deviation was not available [11,20]; and one article included only BCC evaluated using dermoscopy prior to MMS [21]. A randomized open-label study comparing visual inspection, curettage, and dermoscopy in tumor delineation for MMS was excluded because no outcome measure was available for each study group [12]. Contact with the corresponding authors of this study was unsuccessful. Six articles were ultimately included in the present systematic review. Of these, 2 studies were from Asia-Pacific region, 1 from North America, 1 from South America, 1 from Europe, and 1 from Africa (Table 1) [4,6-10].

Description of Included Studies

Of the 6 included studies, 2 were RCTs [6,7], and four were observational studies [4,8-10]. There was no randomized controlled study available for the present systematic review. All included studies were conducted in university-setting centers [4,6-10]. These studies had no funding support and corresponding authors declared no conflicts of interest [4,6-10].

The number of BCCs evaluated ranged from 40 to 197 BCCs per study. The total number of evaluated BCCs was 508. Suzuki et al included both BCC (N = 40) and squamous cell carcinomas (N = 6). The latter were excluded from the analysis. Three studies specified BCC subtypes [6,7,9]. Asilian and Momeni included only nodular BCC [6], and Gurgen and Gatti only infiltrative BCC [7]. Dika et al included various BCC subtypes including nodular (N = 40) and morpheiform BCCs (N = 40) [9].

Recurrent BCCs were excluded in three studies [4,6,7]. One study included only recurrent BCC following ablative laser treatment [10]. Two studies enrolled both primary and recurrent BCC (Table 1) [8,9].

Four studies compared 2 interventions for MMS: tumor delineation using naked eye examination versus dermoscopy-guided margin assessment [4,7,8,10]. One of the studies compared dermoscopy-guided MMS to curettage-guided MMS [9]. Asilian and Momeni compared 3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20) and curettage (N = 20) [6].

For the primary outcome "total margin clearance on the first MMS stage", we assumed that BCCs that underwent more than one Mohs stage showed at least one positive margin. Thereby, the number of BCCs showing total margin clearance on the first MMS stage was extracted from 5 articles [4,7-10].

The secondary outcomes included the mean number of Mohs stages, the recurrence rate, and the number of positive lateral margins after the first Mohs stage.

The mean number of Mohs stages in each study group was specified in 5 articles [4,6-9]. However, related standard deviations were only available in 3 articles [4,6,7]. Contact with the corresponding authors of these studies was unsuccessful. Therefore, we did not have the required data to carry out the up-mentioned analysis for these articles [4,6,7].

Only two studies reported the number of positive lateral margins after the first Mohs stage [4,10].

Relapse rates were described in 2 articles [4,9], ranging between no relapse and 4%, after a follow-up period of 10 ± 5 and more than 62.5 months respectively.

Assessment of Risk of Bias in Included Studies

For RCT [6,7], the Jadad scale was 1 and 2. Overall, the methodological quality was poor. There was no disagreement between the review authors (NL and FH) about the studies quality.

For non-randomized studies [4,8-10], the MINORS index ranged between 14 and 16.

Effects of Interventions

When comparing dermoscopy-guided vs. standard MMS for BCC treatment, there was no statistically significant difference in the proportion of total margin clearance on the first MMS stage (OR 0.86, 95% CI 0.41 to 1.15; five studies [4,7-10]) (Figure 2).

There was no statistically significant difference in the number of Mohs stages when comparing dermoscopy-guided and standard MMS (The standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]) (Figure 3). For this outcome measure, we found heterogeneity (Tau2 = 0220 et I2 = 70.334%). Subgroup analysis was performed based on the technique used for Mohs surgery (frozen sections versus formalin-fixed paraffin-embedded sections). After subgroup analysis, including studies using MMS [6,7], there was no heterogeneity (Tau2 = 0.000), the pooled standard difference in means showed no statistically significant difference. Only one study reported the number of Mohs stages in patients treated using Slow Mohs [4]. Since iterative Mohs sessions rely on histopathological examination of excised tissue, it is possible that the type of tissue processing technique (frozen sections in MMS vs formalin-fixed paraffin-embedded sections in slow Mohs) is responsible for heterogeneity regarding the outcome measure (number of Mohs stages).

A significantly lower proportion of positive lateral margins was obtained with dermoscopy-guided MMS compared with standard MMS based on visual inspection (OR 0.16, 95% CI 0.06 to 0.83; 2 studies [4,10]) (Figure 4).

With regards to recurrence rates, available data was insufficient for meta-analysis. Two studies reported the number of recurrences after MMS [4-9]. One of these

Table 1. Summary of included studies.

Author	Year	Country	Study objective	Study design	Coverage period	Intervention groups	BCC subtypes in each group	Recurrent BCC before Mohs surgery	Cases included in the meta-analysis	Follow-up (months)
Asilian and Momeni [6]	2012	Iran	To compare three ways (naked eye examination, dermoscopy, and curettage) for determining tumor extension before initiation of MMS,	RCT	2011-2012	3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20) and curettage (N = 20)	nodular BCC in all included cases	not included in the study	40	ND
Gurgen and Gatti [7]	2012	United States	To compare the final number of MMS stages performed using dermoscopy and visual inspection of infiltrative basal cell carcinoma	RCT	ND	2 groups: - dermoscopy group (N = 20) - visual inspection group (N = 20)	infiltrative BCC in all cases	not included in the study	40	ND
Suzuki et al [8]	2014	Brazil	To assess the impact of dermoscopy on the demarcation of surgical margins for MMS and ascertain whether the use of this method can shorten operative time	observational study	2009-2011	2 groups: - Group1: Mohs surgery (N = 21) - Group 2: Mohs surgery with dermoscopy-guided margins (N = 23)	ND	Group 1: 3/21 Group 2: 4/23	44	ND

Table 1 continues

Table 1. Summary of included studies. *(continued)*

Author	Year	Country	Study objective	Study design	Coverage period	Intervention groups	BCC subtypes in each group	Recurrent BCC before Mohs surgery	Cases included in the meta-analysis	Follow-up (months)
Dika et al [9]	2017	Italy	to evaluate the role of video-dermoscopy and curettage in MS for a better margin evaluation intraoperatively	observational study	2005-2010	2 groups: - Group 1: Patients treated with video dermoscopy guided Mohs surgery (N = 102) - Group 2: Patients treated with curettage-guided Mohs surgery (N = 95)	Group 1: - nodular BCCs (N = 21) - pigmented BCCs (N = 28) - morpheiform BCCs (N = 20) Group 2: - nodular BCCs (N = 19) - pigmented BCCs (N = 28) - morpheiform BCCs (N = 20) Subtypes of primary tumors (nodular, pigmented, or morpheiform BCCs) were equally distributed in the 2 groups (primary BCC in Group A 71 Group B 69)	Group 1 (31/102) Group 2 (26/95)	197	Group 1 (82.6) Group 2 (62.5)
Shin et al [10]	2020	Korea	To evaluate the usefulness of dermoscopy in determining MMS surgical margins of BCCs with a history of ablative laser treatment.	observational study	2009-2016	2 groups: - Clinical surgical margin (N = 69) - Dermoscopic surgical margin (N = 64)	ND	All cases were recurrent BCC (previously treated by ablative laser). Recurrent cases after radiotherapy or surgical resection were excluded.	133	ND

Author	Year	Country	Study objective	Study design	Coverage period	Intervention groups	BCC subtypes in each group	Recurrent BCC before Mohs surgery	Cases included in the meta-analysis	Follow-up (months)
Litaiem et al [4]	2020	Tunisia	To evaluate the use of dermoscopy in the demarcation of surgical margins in slow Mohs surgery.	observational study	2016-2019	2 groups: G1: tumor demarcation using naked eye examination (N = 28) G2: tumor demarcation using naked eye examination + dermoscopy (N = 26)	ND	not included in the study	54	10 ± 5

BCC = basal cell carcinoma; ND = not described; RCT = randomized clinical trial.

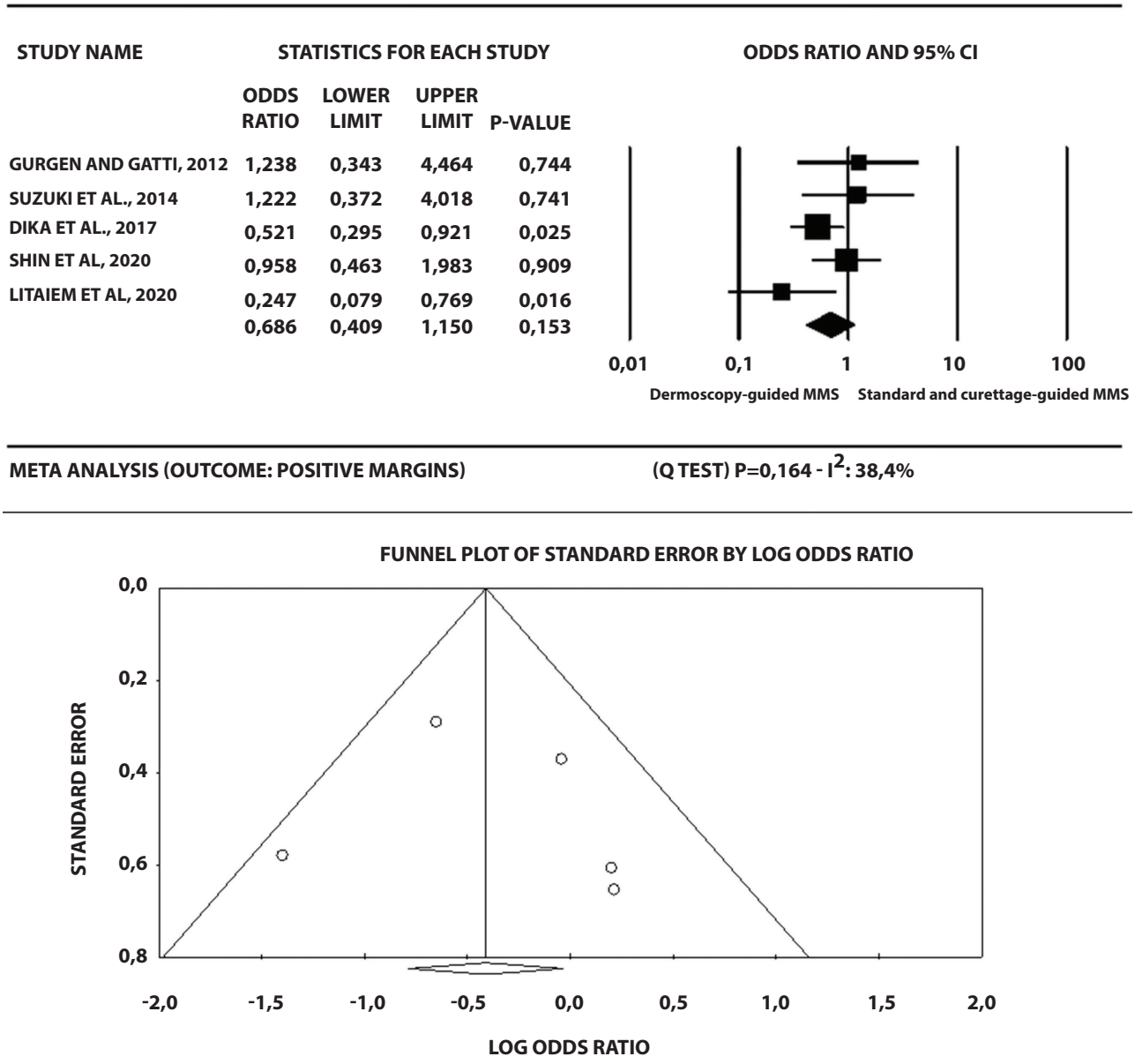


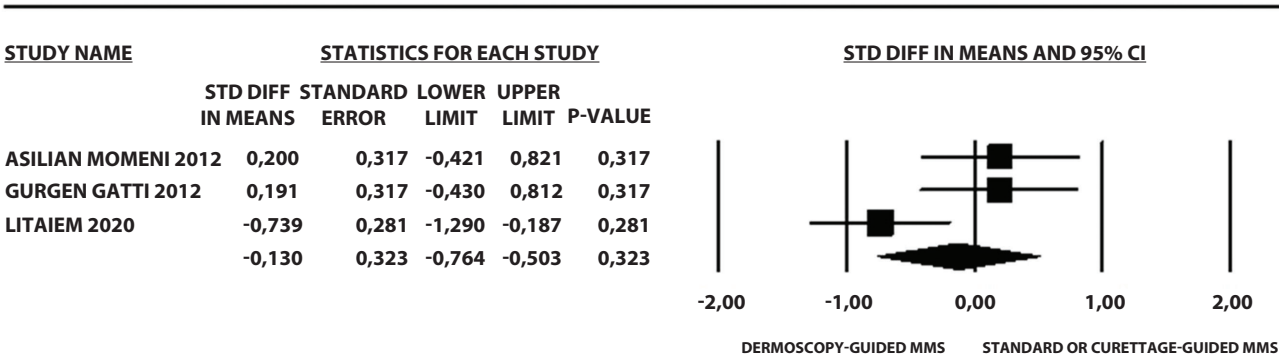
Figure 2. Comparison of the proportion of positive margins after the first Mohs stage using dermoscopy-guided vs. standard or curettage guided MMS for BCC treatment

studies reported a recurrence rate of 3% in BCCs treated with dermoscopy-guided MMS and of 5.2% in those treated with curettage-guided MMS (P = 0.48; Fisher exact test) after a follow-up period of 82.6 and 62.5 months respectively [9]. In the second study, both study groups showed no recurrence after a mean follow-up period of 10 ± 5 months [4].

Conclusions

In the present study, we aimed to assess the effectiveness of dermoscopy as an ancillary tool for MMS. Six studies were included: 2 RCTs [6,7], and 4 observational studies [4,8-10]. The total number of evaluated BCCs was 508. Three studies specified the subtypes of evaluated BCCs [6,7,9]. Three studies excluded recurrent BCC [4,6,7], while one study included only recurrent BCC following ablative laser [10]. Of the included studies, pooling of the data was feasible for 3 evaluated outcomes. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

To the best of our knowledge, no systematic review addressed the question of whether dermoscopy is useful for delineating BCC margins for MMS. Que published a comprehensive narrative review on noninvasive imaging technologies used for the delineation of BCC in the setting of



META ANALYSIS (OUTCOME: NUMBER OF MOHS SESSIONS) **(Q TEST) P=0,034 -I^2: 70,3%**

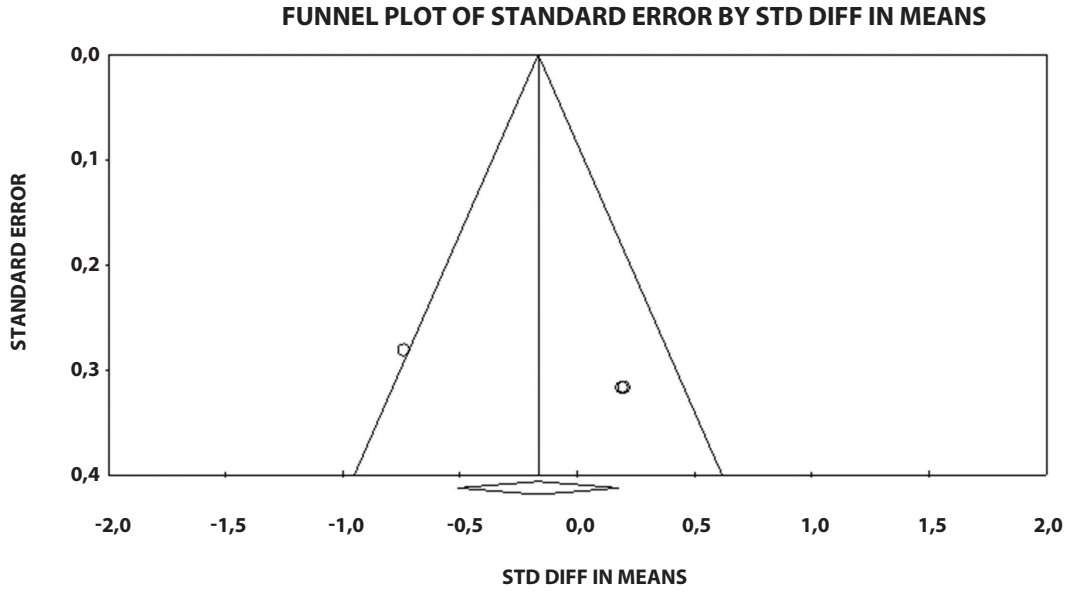
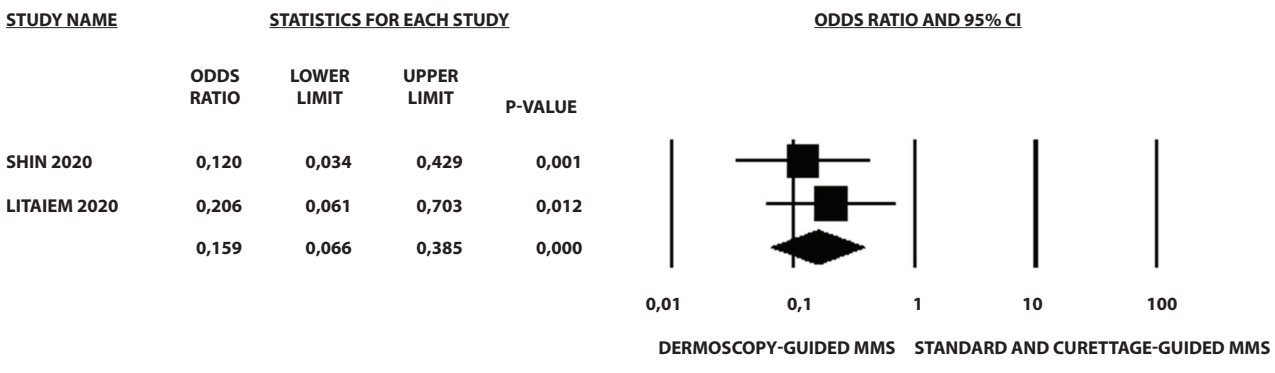


Figure 3. Comparison of the number of Mohs stages using dermoscopy-guided vs. standard or curettage MMS for BCC treatment



META ANALYSIS (OUTCOME: POSITIVE LATERAL MARGINS AFTER THE FIRST MOHS SESSIONS) **(Q TEST) P=0,550 - I^2: 0%**

Figure 4. Comparison of the proportion of positive lateral margins after the first Mohs stage using dermoscopy-guided vs. standard or curettage guided MMS for BCC treatment

MMS [22]. Three technologies were discussed: dermoscopy, confocal microscopy, and optical coherence tomography. Only the number of Mohs stages was evaluated as an outcome measure in relation to dermoscopy. Que stated that dermoscopy did not prove to decrease the number of Mohs stages. In our systematic review, there was no statistically significant difference in the number of Mohs stages between the use of dermoscopy or visual inspection for MMS (the standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]). A hypothesis to explain this finding is that dermoscopy utility is limited to the first Mohs stage. Subsequent stages would only rely on the surgeon's skills and experience.

In the present systematic review, there was no significant association between the use of dermoscopy and the proportion of total margin clearance on the first MMS stage. Surgical margin assessment includes both deep and lateral margin evaluation. A dermoscope is a magnifying instrument that enables visualization of pigmented structures and vessels up to 1mm into the dermis and therefore would not allow for deep margin evaluation [5]. Hence, it is rational to use it for lateral margin evaluation [4,10].

There are several potential implications for both practice and research. Relapsing BCCs and BCCs bearing aggressive histopathological features may exhibit a subclinical extension of their lateral margins [23]. This could result in recurrences and incomplete surgical excision [23]. Further studies assessing lateral margin involvement are needed. In addition, future research is warranted to investigate the utility of dermoscopy for tumor delineation in high-risk BCC.

Combining two imaging techniques is beyond the scope of the present systematic review. Recently, Lupu et al evaluated whether BCC lateral excision margins could be precisely evaluated preoperatively through the use of dermoscopy and reflectance confocal microscopy [23]. In this study, 18 patients (20 BCCs, mostly were nodular: 12/20) were included. The authors concluded that dermoscopy served as an accurate guide during reflectance confocal microscopy [23]. The global accuracy of the procedure was 93.1% (95% CI 0.77–0.99) [23].

The present systematic review sought to summarize the existing data on the possible use of dermoscopy for tumor delineation in MMS. However, certain limitations apply to the results depicted herein. First, our sample size was limited by the scarcity of research on this subject in the literature. Only two included studies evaluated the use of dermoscopy for lateral margin assessment. Therefore, these results should be interpreted with caution. Second, some studies had missing data on outcome measures and hence were excluded from the data analysis. Third, the histopathological subtype of BCC, which can act as a confounding factor, was not indicated in all included studies. This may hinder the interpretation of findings and undermine their accuracy. Finally, both dermoscopy and MMS are operator-dependent procedures [4]. Thus, controlled, consistent and reproducible results are not readily attainable.

Despite these limitations, this systematic review is a comprehensive summary on the reported use of dermoscopy for BCC delineation in MMS to date. Overall, our data suggest that dermoscopy could improve lateral margin assessment within the first Mohs stage. Future randomized clinical trials are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.

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