




The Diagnostic Accuracy of *Ex Vivo* Confocal Laser Scanning Microscopy for Basal Cell Carcinoma: A Systematic Review and Meta-analysis

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This systematic review and meta-analysis evaluated available data on the diagnostic accuracy of *ex vivo* confocal laser scanning microscopy (EVCM) for the diagnosis of basal cell carcinoma (BCC) in tissue specimens and for margin assessment in micrographic surgery, using conventional histopathological analysis as reference standard. MEDLINE and Embase were systematically searched in November 2024 in accordance with PRISMA guidelines to identify diagnostic accuracy studies evaluating EVCM for BCC. Pooled sensitivity and specificity were estimated using bivariate random-effects models. Sixteen studies comprising 1,387 specimens were included. The pooled mean EVCM acquisition time was 7.0 min (95% confidence interval [CI]: 5.3–9.4). For BCC diagnosis in tissue specimens, pooled sensitivity was 91.4% (95% CI: 85.9–94.9) and pooled specificity was 91.1% (95% CI: 79.2–94.5). Regarding margin assessment, pooled sensitivity and specificity were 79.5% (95% CI: 65.0–89.0) and 92.2% (95% CI: 85.5–95.9). In conclusion, EVCM shows high sensitivity and specificity for BCC diagnosis in tissue specimens and may selectively replace conventional histology when rapid diagnosis is desired. For margin assessment, EVCM has high specificity but moderate sensitivity. Therefore, conventional histology should still be considered as a subsequent step, particularly after the final excision stage of stepwise micrographic surgery.

Key words: basal cell carcinoma; confocal laser scanning microscopy; diagnostic accuracy; dermatologic surgical procedures; Mohs surgery; meta-analysis.

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Basal cell carcinoma (BCC) is the most frequently occurring skin cancer in fair-skinned populations, comprising around 3 quarters of all diagnosed skin

SIGNIFICANCE

Basal cell carcinoma (BCC) is the most common skin cancer. By identifying and analysing published data, we aimed to find out how accurate a newer microscope technique, called *ex vivo* confocal laser scanning microscopy (EVCM), is for diagnosing BCC and checking whether the cancer has been completely removed during surgery. We found that EVCM correctly diagnosed BCC in about 9 out of 10 tissue samples. When used to assess surgical margins, tumour involvement and thus the need for re-excision was correctly identified in about 8 out of 10 cases and consequently missed in about 2 out of 10 cases.

cancers (1). Although its metastatic potential is low, BCC is locally invasive and can cause significant morbidity if not adequately excised (2).

In the diagnostic work-up of suspected BCC, a punch or shave biopsy is typically performed to establish histopathological confirmation. Upon verification of the diagnosis, margin-controlled (micrographic) surgery is commonly employed in high-risk tumours in critical anatomical sites like the face to achieve complete tumour clearance while minimizing removal of uninvolved tissue (3).

The current gold standard for diagnosis and margin control is the histopathological evaluation of formalin-fixed, paraffin-embedded tissue. However, this process is time-consuming and resource-intensive, thereby limiting intraoperative decision-making. To enable intraoperative assessment of tumour-free margins, Mohs micrographic surgery was developed. In Mohs micrographic surgery, cryoconserved (frozen) tissue sections are prepared and examined intraoperatively, allowing evaluation of the entire peripheral and deep margins of the excised specimen. If residual tumour is detected, the procedure is performed in a stepwise manner with additional excision stages until tumour-free margins are achieved. This technique combines complete margin control with maximal preservation of healthy tissue (4).

In recent years, *ex vivo* confocal laser scanning microscopy (EVCM) has emerged as a promising imaging modality that enables real-time microscopic

visualization of freshly excised tissue without the need for cryoconservation or conventional staining. This technique therefore has the potential to facilitate intraoperative margin assessment more rapidly and with fewer resources. EVCM provides optical sections of skin structures at a resolution comparable to that of traditional histopathology, allowing for the identification of characteristic BCC features such as tumour nests, peripheral palisading and stromal clefting (5–7). Several studies have investigated the sensitivity and specificity of EVCM for both the diagnosis and margin assessment of BCC.

The aim of this systematic review and meta-analysis was to synthesize data from existing studies on the diagnostic accuracy of EVCM for the diagnosis of BCC in tissue specimens and for margin assessment in micrographic surgery, to better define its clinical applicability.

MATERIALS AND METHODS

Protocol registration and reporting standards

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of Diagnostic Test Accuracy Studies guidelines (8). The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID CRD42024601458.

Search strategy and study selection

A systematic literature search was conducted in MEDLINE and Embase (via Ovid) on 1 November 2024 to identify studies evaluating the diagnostic accuracy of EVCM in the diagnosis and/or margin assessment of BCC. The complete search string is provided in Table SI. In addition to the database search, the reference lists of eligible studies were reviewed, and experts in the field were contacted to identify potentially relevant studies.

Studies were eligible for inclusion if they

- investigated the diagnostic accuracy of EVCM for the diagnosis of BCC in tissue specimens and/or margin control in micrographic surgery
- reported a 2×2 contingency table or provided sufficient information to reconstruct one and
- used formalin-fixed paraffin-embedded or cryoconserved histology as the reference standard.

Studies were excluded if the EVCM evaluation was performed exclusively by artificial intelligence or automated image analysis without human expert validation.

No restrictions regarding publication year were applied. Conference abstracts, case reports, review articles and opinions were excluded. In addition, studies that included fewer than 10 cases of BCC were excluded.

Data extraction

Two reviewers (S.L. and L.M.) independently extracted data from the included studies using a predefined data extraction form. Extracted variables included study design; patient and lesion characteristics; specimen preparation method (punch, shave, bread loaf excision, or micrographic excision using Mohs procedure (9, 10), randstrip method = “Tuebinger Torte” (11), muffin technique (11) or other); EVCM device type; EVCM acquisition time; and the number of true positives, false positives, false negatives and true negatives.

All extracted data were cross-checked for accuracy and consistency between the reviewers. In cases of ambiguous or inconsistent information, the corresponding authors of the original publications were contacted for clarification. Disagreements between reviewers were resolved through discussion, and if necessary, arbitration by a third reviewer (B.K.).

Data synthesis and statistical analysis

All statistical analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Analyses were conducted by one author (B.K.), who holds an M.Sc. in Biostatistics, using the meta (12) and mada R packages (13).

Continuous variables such as mean age of included patients and mean EVCM acquisition time were pooled using random-effects meta-analysis models for continuous outcomes. Pooled proportions of histological subtypes (nodular, sclerodermiform, superficial/multifocal and others) and tumor localizations (head/neck, trunk, extremities and other sites) were estimated using random-effects models for proportions.

Bivariate random-effects models following the Reitsma et al. framework (14) were applied to pool sensitivity and specificity estimates of EVCM with formalin-fixed paraffin-embedded or cryoconserved histology as the reference standard. Analyses were conducted separately for diagnostic detection of BCC in punch, shave and broad leaf excision specimens, and for margin assessment in micrographic excisions.

To explore heterogeneity in diagnostic accuracy across different micrographic surgery techniques, subgroup analyses using meta-regression models were applied to assess differences in the diagnostic performance of EVCM between the following methods: Mohs micrographic surgery (9, 10), the randstrip

method (“Tübinger Torte”) (11) and the muffin technique (11).

A robustness analysis/sensitivity analysis was performed to assess the stability of the results and to determine whether the diagnostic performance estimates were consistent across different EVCM device generations. This analysis compared earlier- vs newer-generation EVCM devices for both BCC diagnosis in tissue specimens and margin assessment using meta-regression models to evaluate potential differences in accuracy between device generations.

An alpha level of 0.05 was considered statistically significant for all analyses.

Risk of bias assessment

The risk of bias and applicability concerns for each included study were evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (15). Two reviewers (S.L. and L.M.) independently assessed four domains: patient selection, index test, reference standard and flow and timing. For each domain, risk of bias was rated “low”, “high” or “unclear”, applicability concerns were considered for the first three domains. Discrepancies were resolved by consensus, with a third reviewer consulted (B.K.) if agreement could not be reached.

Potential publication bias was assessed visually using funnel plots of diagnostic odds ratios from studies evaluating the diagnostic accuracy of EVCM for BCC diagnosis in tissue specimens and for margin assessment. Funnel plot asymmetry was formally tested using the Harbord regression test (16).

Certainty of evidence assessment

The certainty of the evidence for each pooled diagnostic accuracy measure was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework for diagnostic tests (17). The certainty of evidence for a pooled effect estimate was downgraded when substantial heterogeneity was present among the included effect estimates, when the pooled estimate showed wide confidence intervals, when several studies with a high risk of bias in the 5 domains were included in the analysis, or when publication bias was detected.

RESULTS

Study selection

The electronic database search yielded 880 records, which were screened by title and abstract. Of these, 155 full-text articles were assessed for eligibility. Ultimately, 16 studies met the inclusion criteria and were included

in the quantitative synthesis (5, 7, 11, 18–30). The study selection process is summarized in the PRISMA flow diagram (Fig. 1).

Study characteristics

The 16 included studies comprised a total of 1,387 specimens. The majority of specimens were excised from the head and neck region (91.8%; 95% CI [confidence interval]: 76.0–97.5). Nodular BCC was the most common histopathological subtype (45.3%; 95% CI: 33.8–57.3), followed by sclerodermiform/micronodular BCC (30.1%; 95% CI: 17.8–45.9), superficial BCC (10.8%; 95% CI: 6.6–17.2) and other forms. Overall, 15.9% of specimens were free of BCC (95% CI: 7.1–31.9). The mean age of included patients was 73.2 years (95% CI: 71.5–74.9), and 41.6% (95% CI: 36.3–47.0) were female.

Twelve studies utilized the VivaScope® 2500 microscope (Lucid Inc., Rochester, USA), one study used the VivaScope® 2000, one study applied a strip-mosaicing confocal microscope based on VivaScope® technology, one study employed the Histolog® Scanner V1 (SamanTree Medical SA, Awans, Belgium) and one used the Histolog® Scanner V2. The pooled mean EVCM acquisition time was 7.0 min (95% CI: 5.3–9.4).

Diagnostic accuracy for BCC diagnosis in tissue specimens

Seven studies reported the diagnostic accuracy for EVCM in BCC diagnosis using punch, shave or bread-loaf excision specimens. Forest plots of individual study sensitivities and specificities are presented in Figs. S1 and S2, respectively. The pooled sensitivity was 91.4% (95% CI: 85.9–94.9), and the pooled specificity was 91.1% (95% CI: 79.2–94.5). Between-study heterogeneity was low ($I^2=5.2\%$). The summary receiver operating characteristic (SROC) curve is shown in Fig. 2.

Given the low heterogeneity, relatively narrow confidence intervals, absence of major concerns regarding risk of bias in most studies included in this analysis (Table SII and Fig. S3) and the lack of evidence for publication bias (Fig. S4), the certainty of evidence for diagnostic detection was rated as high according to the GRADE framework.

Diagnostic accuracy for margin assessment in micrographic surgery

Twelve studies investigated the diagnostic accuracy of EVCM for margin assessment of BCC in the context of micrographic surgery. Forest plots of sensitivities and specificities are shown in Figs S5 and S6. The pooled sensitivity for margin assessment was 79.5% (95%

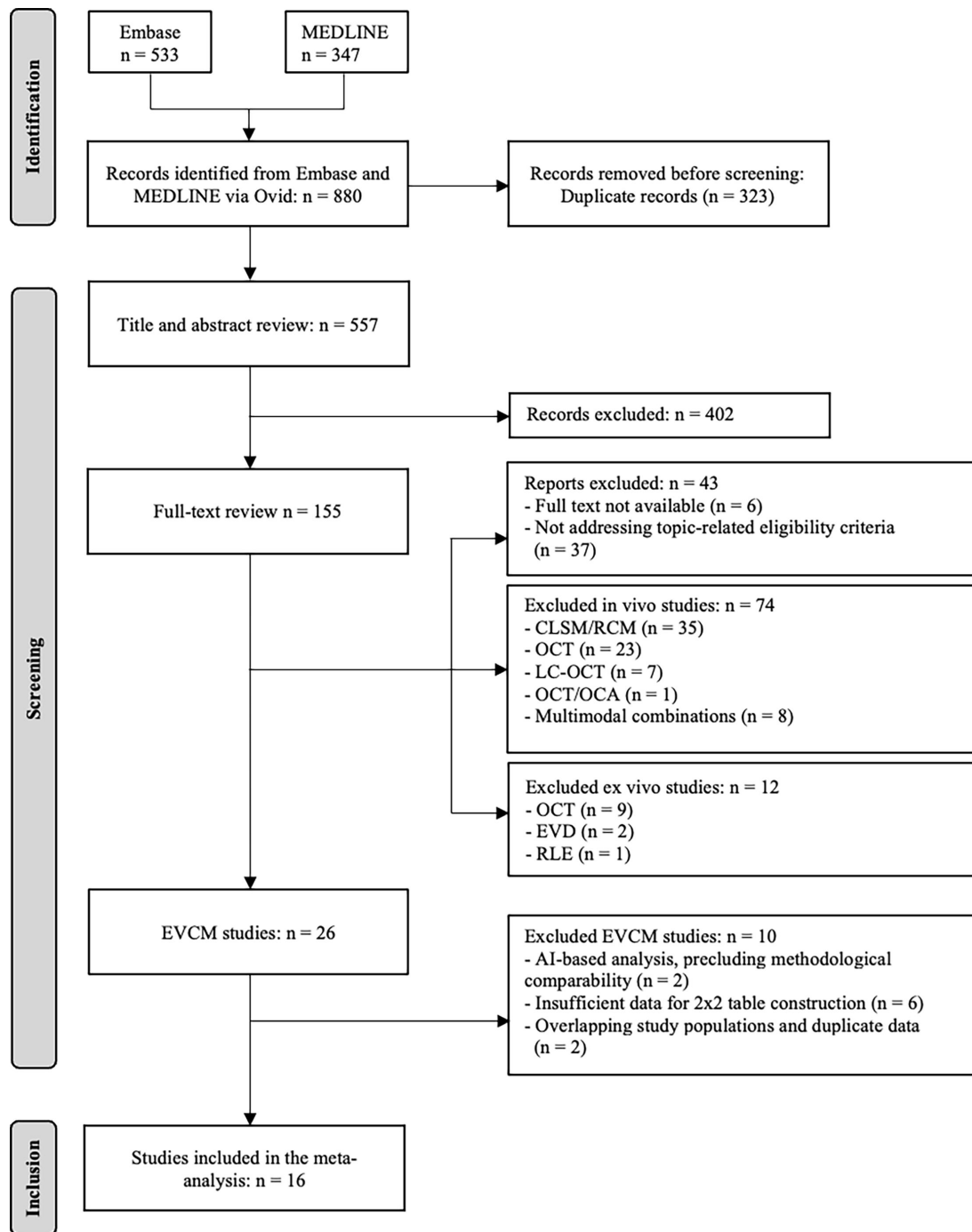


Fig. 1. Screening of References. PRISMA flow diagram summarizing the study selection process structured into 3 phases: identification, screening and inclusion. Screening the reference lists of included studies and contacting experts in the field did not reveal additional eligible studies. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CLSM: confocal laser scanning microscopy; RCM: reflectance confocal microscopy; OCT: optical coherence tomography; LC-OCT: line-field optical coherence tomography; OCA: optical coherence angiography; EVD: *ex vivo* dermoscopy; RLE: Rapid Lump examination.

CI: 65.0–89.0), and the pooled specificity was 92.2% (95% CI: 85.5–95.9), with moderate heterogeneity ($I^2=13.8\%$). The SROC curve is shown in **Fig. 3**.

Given the moderate heterogeneity, acceptably narrow confidence intervals, absence of major concerns regarding risk of bias in most studies included in this analysis (Table SII and Fig. S3), and the lack of

evidence for publication bias (Fig. S7), the certainty of evidence for margin assessment was rated as high according to the GRADE framework.

Subgroup analysis by micrographic surgery technique. Subgroup analyses were conducted to explore heterogeneity across micrographic surgery techniques for margin assessment. When the Mohs micrographic

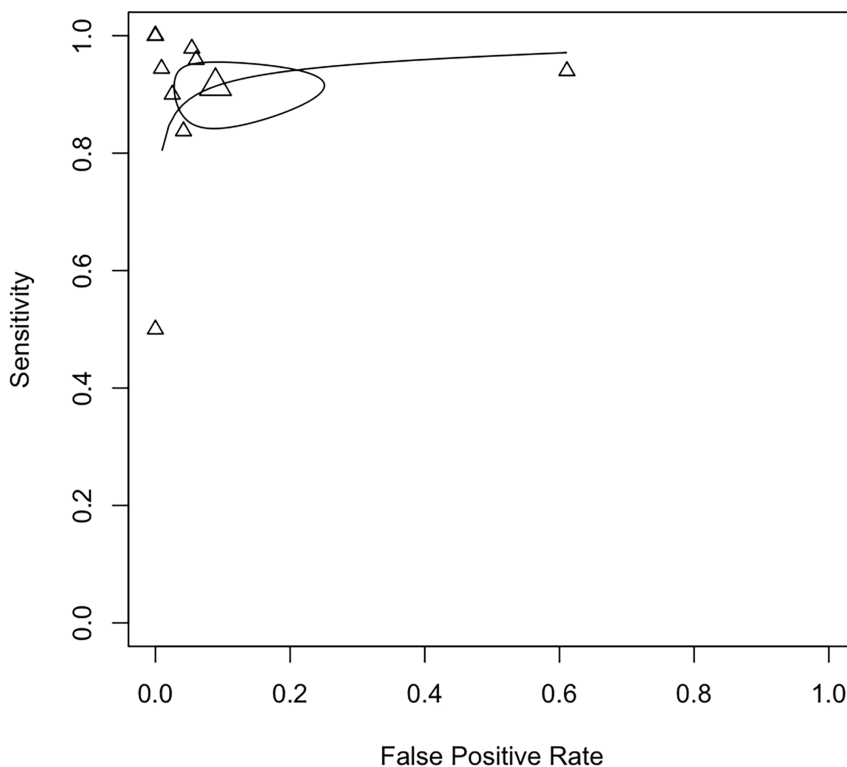


Fig. 2. Summary receiver operating characteristic (SROC) curve for the diagnostic accuracy of *ex vivo* confocal microscopy (EVC) in the diagnosis of basal cell carcinoma (BCC) in tissue specimens. The solid line represents the SROC curve, illustrating the trade-off between sensitivity and the false-positive rate across the included studies, with each triangle representing an individual study estimate. The solid oval indicates the 95% confidence region around the summary estimate (large triangle). The false-positive rate is mathematically equivalent to $1 - \textit{specificity}$.

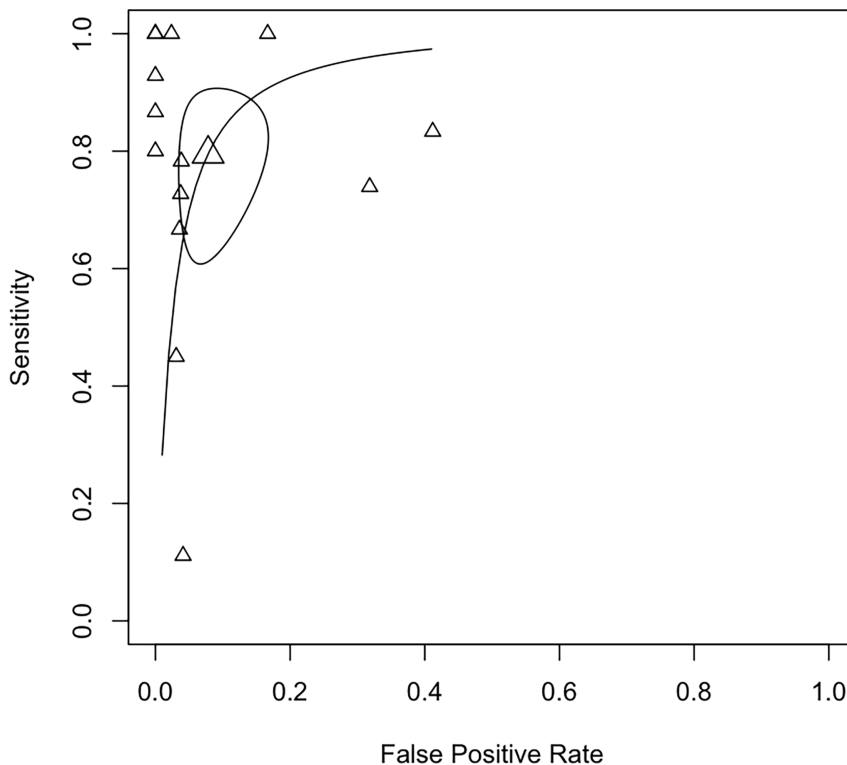


Fig. 3. Summary receiver operating characteristic (SROC) curve for the diagnostic accuracy of *ex vivo* confocal microscopy (EVC) in the margin assessment in micrographic surgery of basal cell carcinoma (BCC). The solid line represents the SROC curve, illustrating the trade-off between sensitivity and the false positive rate across the included studies, with each triangle representing an individual study estimate. The solid oval indicates the 95% confidence region around the summary estimate (large triangle). The false-positive rate is mathematically equivalent to $1 - \textit{specificity}$.

surgery procedure was used, the pooled sensitivity was 87.6% (95% CI: 44.9–98.4) and the pooled specificity was 93.8% (95% CI: 85.5–97.4; $I^2=26.4$). For the margin-strip technique (“Tübinger Torte”), the pooled sensitivity was 67.9% (95% CI: 52.1–80.5) and the pooled specificity was 93.3% (95% CI: 79.4–98.1; $I^2=37.1$). For the muffin technique, the pooled sensitivity was 76.1% (95% CI: 34.1–95.1) and the pooled specificity was 85.6% (95% CI: 25.0–99.1; $I^2=0$). The SROC curves for these subgroups are presented in **Fig. 4**. No statistically significant differences in sensitivity or specificity were observed between excision techniques ($p>0.05$).

The GRADE certainty of evidence was downgraded to moderate for the Mohs and margin-strip subgroups and to low for the muffin technique due to wide confidence intervals.

Robustness analysis

A sensitivity analysis was performed to compare diagnostic performance between EVCM devices of earlier and newer generations. For BCC diagnosis in tissue specimens, newer-generation devices (VivaScope® 2500 and Histolog® Scanner V2) demonstrated a significantly higher pooled

sensitivity of 93.9% (95% CI: 90.6–96.1) compared with older-generation devices (VivaScope® 2000 and Histolog® Scanner V1), which showed a sensitivity of 83.0% (95% CI: 73.7–89.5; $p=0.002$). The pooled specificity did not differ significantly between generations (newer: 90.0%, 95% CI: 71.4–97.0; older: 93.7%, 95% CI: 80.6–98.2).

For margin assessment, the pooled sensitivity with newer-generation devices was 80.0% (95% CI: 64.2–89.9), compared to 77.8% (95% CI: 22.7–97.7) for older-generation devices. This difference was not statistically significant. Similarly, pooled specificity did not differ significantly between device generations (newer: 92.4%, 95% CI: 82.7–96.8; older: 93.2%, 95% CI: 79.9–97.9).

Summary of key findings

The key findings are summarized in **Table I**.

DISCUSSION

Conventional histopathological examination of resected tissue is the reference standard for diagnosis and margin control of BCC (31). To extend diagnostic capabilities and develop more time-efficient intraoperative tools,

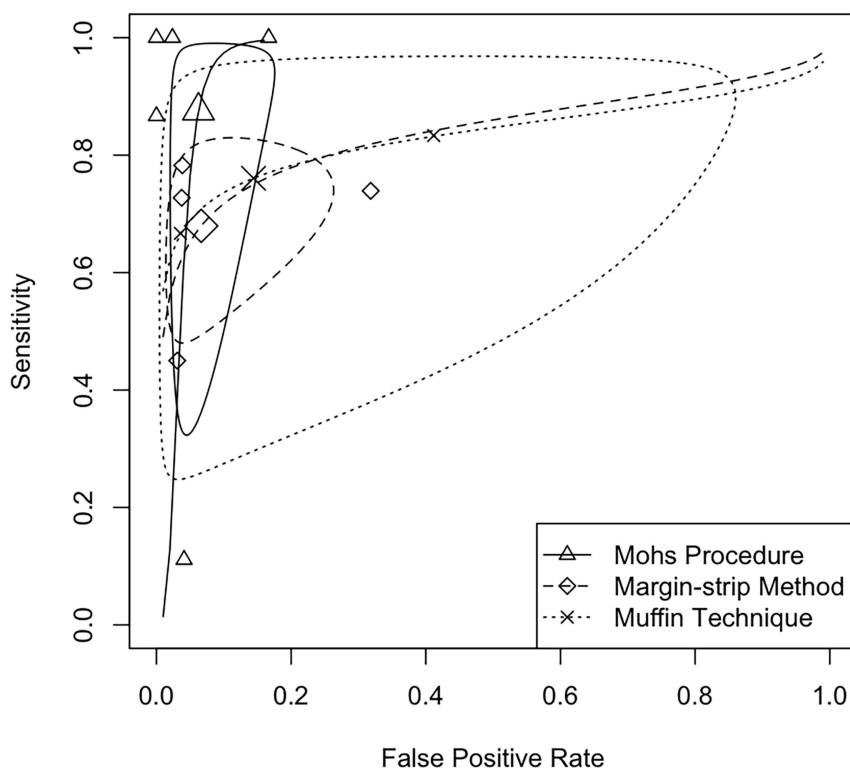


Fig. 4. Summary receiver operating characteristic (SROC) curve for the diagnostic accuracy of *ex vivo* confocal microscopy (EVCM) in the margin assessment in micrographic surgery of basal cell carcinoma (BCC), subgrouped by excision technique. The solid, dashed and dotted lines represent the SROC curves, illustrating the trade-off between sensitivity and the false-positive rate across the included studies. Each triangle, diamond and cross represents an individual study estimate corresponding to a specific excision technique. The solid, dashed and dotted ovals indicate the 95% confidence regions around the respective summary estimates (large triangle, diamond or cross). The false positive rate is mathematically equivalent to $1 - \text{specificity}$.

Table I. Summary of diagnostic accuracy measures of EVCM for BCC

Outcome	pooled sensitivity, % (95% ci)	Pooled specificity, % (95% CI)	I ² , %	GRADE certainty of evidence
BCC diagnosis in tissue specimens	91.4 (85.9–94.9)	91.1 (79.2–94.5)	5.2	High
Margin assessment in micrographic surgery	79.5 (65.0–89.0)	92.2 (85.5–95.9)	13.8	High
Mohs procedure	87.6 (44.9–98.4)	93.8 (85.5–97.4)	26.4	Moderate
Margin-strip method (“Tübinger Torte”)	67.9 (52.1–80.5)	93.3 (79.4–98.1)	37.1	Moderate
Muffin technique	76.1 (34.1–95.1)	85.6 (25.0–99.1)	0.0	Low

BCC: basal cell carcinoma; CI: confidence interval; EVCM: ex vivo confocal microscopy; GRADE: Grading of Recommendations Assessment, Development, and Evaluation framework.

EVCM has emerged as a promising approach to accelerate and streamline surgical workflows (5–7). In this context, we conducted a systematic review and meta-analysis aiming to estimate the diagnostic accuracy of EVCM for BCC diagnosis in tissue specimens and margin assessment in micrographic surgery.

Our results are based on 16 studies encompassing a total of 1,387 excised specimens. Seven studies evaluated the diagnostic accuracy for BCC diagnosis in tissue specimens and 12 studies assessed margin control. EVCM correctly diagnosed the presence or absence of BCC in approximately 9 out of 10 tissue specimens. In contrast, diagnostic accuracy for margin assessment was lower. EVCM detected tumour-free margins in around 9 out of 10 cases during micrographic surgery, whereas tumour involvement of the excision margin was detected in approximately 8 out of 10 cases. No statistically significant differences in sensitivity or specificity were observed between micrographic surgery techniques; however, the certainty of the evidence was reduced due to wide confidence intervals. When comparing EVCM device generations, sensitivity for BCC diagnosis in tissue specimens was significantly higher with newer-generation devices than with earlier models, while specificity remained comparable. No significant differences were observed for margin assessment.

Comparison with relevant literature

Given the current state of research, most existing review articles on EVCM in this field are qualitative in nature, focusing on technical aspects, characteristic imaging features and the discussion of its potential role as an intraoperative pathology tool (32–34). Ge, Cherian and Dang presented an abstract of a systematic review and meta-analysis on the diagnostic accuracy of EVCM for margin assessment of BCC at the Australasian College of Dermatologists 55th Annual Scientific Meeting in 2023 (35) however, no corresponding journal publication of this work could be identified in MEDLINE or Embase.

Most available evidence summarizing the use of confocal laser scanning microscopy in dermatologic surgery focuses on *in vivo* applications (36, 37). Lupu et al. (36) conducted a comprehensive systematic review and meta-analysis on the

diagnostic accuracy of *in vivo* confocal laser scanning microscopy for BCC, reporting pooled sensitivity and specificity estimates of 92% and 93%, respectively. These values are comparable to the pooled sensitivity and specificity derived from the *ex vivo* data included in our systematic review and meta-analysis, although heterogeneity was substantially higher in the *in vivo* studies.

Clinical implications

For the diagnosis of BCC in skin tissue specimens such as punch or shave samples, EVCM demonstrates high sensitivity and specificity, correctly identifying the presence or absence of tumour in approximately 9 out of 10 cases. This high level of diagnostic accuracy suggests that EVCM could selectively replace conventional histology in certain scenarios where rapid diagnosis is desired to enable prompt surgical intervention.

For margin assessment, EVCM demonstrates high specificity but moderate sensitivity, with tumour involvement correctly identified in approximately 8 out of 10 cases. Consequently, tumour extension at the surgical margin may be missed in around 2 out of 10 cases. This level of uncertainty does not yet support the use of EVCM as a stand-alone method for intraoperative margin control. Therefore, conventional histology should be considered as a subsequent step, at least after the final excision stage in stepwise micrographic surgery, to ensure detection and appropriate management of any tumour extensions missed by EVCM.

Strengths and limitations

To our knowledge, this systematic review and meta-analysis represents the first comprehensive quantitative synthesis of the diagnostic accuracy of EVCM for both BCC diagnosis in tissue specimens and margin assessment in micrographic surgery. The study was conducted according to established methodological standards for diagnostic test accuracy reviews, including prospective protocol registration in PROSPERO, adherence to PRISMA guidelines and use of the QUADAS-2 and GRADE frameworks to assess risk of bias and certainty of evidence. The application of bivariate random-effects models allowed joint pooling of sensitivity and specificity while accounting for their

interdependence. In addition, subgroup and robustness analyses provided insight into potential sources of heterogeneity, including different micrographic surgery techniques and EVCM device generations, thereby strengthening the interpretability and clinical relevance of the findings.

Several limitations should also be acknowledged. First, subgroup estimates for individual micrographic surgery techniques were based on a limited number of studies, resulting in wide confidence intervals and reduced certainty of evidence. Second, most included studies were single-centre investigations conducted under experimental or semi-controlled conditions, which may limit generalizability to routine clinical practice. Third, institutional clustering may represent a potential source of bias, as several included studies originated from research within our institution. Fourth, the literature search was limited to 2 databases rather than 3 or more, which may have reduced the comprehensiveness of study identification.

Future research

Future research should focus on improving the diagnostic accuracy of EVCM for margin assessment, as current performance does not yet support its use as a stand-alone method for intraoperative margin control.

In addition, future studies should explore integrated diagnostic workflows, including the potential role of *in vivo* confocal laser scanning microscopy (IVCM) in identifying lesions that are particularly suitable for EVCM (38), not only for detection but also for subtype classification and assessment of tumour extent. Such preselection may increase pretest probability, potentially further enhance diagnostic accuracy of EVCM and enable nonsurgical treatment of superficial or flat nodular BCC.

The integration of artificial intelligence is expected to become increasingly relevant for advancements in imaging technology and image interpretation, for example by enhancing consistency and reducing dependency on reader expertise (39).

Conclusion

EVCM demonstrates high sensitivity and specificity for the diagnosis of BCC in punch and shave biopsies and may selectively replace conventional histology in scenarios where rapid diagnosis is desired to enable prompt surgical intervention.

For margin assessment, EVCM shows high specificity but moderate sensitivity. Therefore, conventional histology should currently still be considered as a subsequent step, at least after the final excision stage in stepwise micrographic surgery.

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Data availability statement: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request. Access to the data will be granted for legitimate academic purposes.

Ethics committee: Ethical approval was not required for this systematic review and meta-analysis, as it relied solely on previously published and anonymized data.

The authors have no conflicts of interest to declare.

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