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Review Article

Novel imaging techniques for tumor margin detection in basal cell carcinoma: a systematic scoping review of FDA and EMA-approved imaging modalities

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Abstract

Mohs micrographic surgery (MMS) is the gold standard for removing basal cell carcinomas (BCCs) due to its ability to guarantee 100% margin evaluation through frozen section histopathology, offering the highest cure rate among current treatments. However, noninvasive imaging technologies have emerged as promising alternatives to clinical assessment for defining presurgical margins. This systematic scoping review examines the efficacy of these imaging modalities, focusing on those approved for clinical use by the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA). A systematic search of EMBASE, Scopus, PubMed, and the Cochrane Public Library databases identified 11 relevant studies out of 2123 records, encompassing 644 lesions across five imaging techniques. The findings suggest that dermoscopy, high-frequency ultrasound (HFUS), optical coherence tomography (OCT), line-field optical coherence tomography (LC-OCT), and reflectance confocal microscopy (RCM) show potential in detecting BCC margins, which could enhance MMS by providing better preoperative planning, informing patients of expected defect size, aiding in reconstruction decisions, and reducing overall procedure costs. This review discusses the benefits and limitations of each technique, offering insights into how these innovations could influence the future of BCC management. Emerging imaging techniques could enhance MMS by improving BCC margin assessment and reducing costs. Their adoption will depend on price and ease of use.

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Introduction

Basal cell carcinoma (BCC) is the most common skin cancer and also the most common human malignancy in fair-skinned populations.[1] The incidence of BCC is on the rise.[2] Over 3 million BCCs are diagnosed in the US annually, posing a significant burden on the healthcare system and considerable quality of life issues for patients.[3] BCCs usually arise from sun exposure and manifest with various clinical variants, including nodular BCC characterized by a pearly or waxy papule, superficial BCC presenting as a flat, erythematous, or brown, scar-like macule, and morpheaform (or infiltrative) BCC, which appears as a firm, flat, or slightly depressed lesion with indistinct borders. Additionally, BCCs can present as pigmented variants or as persistent ulcers that may bleed.[1,4] BCCs display various architectural patterns like superficial, nodular, micronodular, and infiltrative growth, representing the main histological subtypes.[5,6] They often occur on sun-damaged skin with multiple scars from past surgeries, complicating margin definition during clinical assessment, especially when coexisting with other skin lesions like seborrheic keratosis, nevus sebaceous, and actinic keratoses.[7,8] Furthermore, BCC often exhibits subclinical extension and skip lesions, complicating both clinical and standard histological margin determination.[9]

Mohs micrographic surgery (MMS) is a precise technique involving systematic removal and immediate histological examination of cancer-containing skin. MMS ensures complete margin evaluation, which is particularly beneficial for cancers in critical areas like the face, hands, and genitals, minimizing healthy tissue removal for improved cosmetic outcomes.[10,11] MMS aims to achieve negative margins prior to reconstruction while minimizing the amount of normal tissue resected. Tumors can have a subclinical extension and may require additional stages to achieve tumor-free margins. As additional stages are needed, the cost of the procedure increases. Being able to predict better the tumor extent preoperatively can decrease the number of stages and, therefore, reduce the time and expense of the procedure.

Innovative preoperative assessment tools can potentially enhance the precision of MMS, particularly in complex or borderline cases. While MMS is well-established and reimbursed in some countries, leading to its use even for small, simple BCCs, integrating advanced imaging techniques could help distinguish which cases truly require MMS versus simpler excision.[12] By improving preoperative planning, these tools can guide the decision-making process, potentially reducing unnecessary MMS procedures for straightforward cases and thereby controlling costs. Advanced imaging could provide critical information for more challenging or ambiguous cases, ensuring that MMS is used judiciously and effectively.[12]

Mounting data indicates that certain imaging techniques can assist or even replace histological sampling.[13,14] The burgeoning field of noninvasive imaging techniques in dermatology includes clinically approved and investigational modalities such as dermoscopy,[15] high-frequency ultrasound (HFUS),[16–18] optical coherence tomography (OCT),[19,20] line-field confocal optical coherence tomography (LC-OCT),[21] reflectance confocal microscopy (RCM),[22] multispectral imaging[23] and Raman spectroscopy.[24] However, limited information exists on the utility of imaging for determining residual tumor margins. *In vivo* imaging could revolutionize dermatologic surgery by providing real-time visualization and analysis of tumor depth and boundaries presurgery, potentially optimizing outcomes in MMS through refined precision and streamlined processes. Our review concentrates on noninvasive imaging techniques potentially useful in assessing BCC margins. In this systematic scoping review, we aimed to fill critical gaps left by previous reviews by specifically addressing all Food and Drug Administration (FDA)[25] and European Medicines Agency (EMA)[26] approved techniques, ensuring relevance and applicability in real-world clinical settings. We offer dermatologists a comprehensive overview of these techniques' utility in margin determination, covering their capability in detecting BCC, addressing penetration depth, resolution, imaging speed, contrast source, detected signal background, clinical applications, advantages, and

limitations. We also assess the considerable limitations in the current literature to aid new projects aiming to provide clinically meaningful data.

Materials and methods

Literature search

Scoping reviews like those in this study are not registered on PROSPERO. All study procedures, however, strictly followed the PRISMA Extension for Scoping Reviews (PRISMA-Scr) checklist, and adherence to the guidelines was maintained throughout.[27] Searches were conducted from December 4, 2023, to December 15, 2023, using EMBASE, Scopus, PubMed, and Cochrane databases without imposing any restrictions on publication dates. The search was re-run before the final analysis on February 1, 2024, to identify any further studies. The search strategy employed specific search terms combined with Boolean operators. Boolean operators are words such as AND and OR that are NOT used in search queries to combine or exclude keywords, thereby refining and focusing search results. The search strategy included the terms 'basal cell carcinoma' AND (border OR depth OR margin OR margins OR mapping OR Mohs OR histopathological OR monitoring) AND ("dermatoscopy" OR "dermoscopy" OR "optical coherence tomography" OR "reflectance confocal microscopy" OR "laser scanning confocal microscopy" OR "ultrasound").

Selection criteria

The PICO (Patient, Intervention, Comparison, Outcome) model was employed to structure and address the clinical question. The criteria were as follows:

- P (Patient): Individuals diagnosed with BCC
- I (Intervention): FDA or EMA-approved noninvasive imaging technologies
- C (Comparison): Histopathology
- O (Outcome): Efficacy for detecting BCC tumor borders, including sensitivity, specificity, and positive and negative predictive value

Selected studies included observational studies, retrospective or prospective studies, case series, and randomized designs that met the PICO eligibility criteria.

Exclusion criteria included pediatric, preclinical, and animal studies, narrative reviews, letters to the editor, meeting abstracts, case reports, studies not in English, and studies lacking data of interest, not focusing on the target outcome, or without full text.

Agreement assessment in retrieved studies

All retrieved studies underwent screening by two independent authors: M.B. (located in Budapest, Hungary) and S.B. (located in Buffalo, New York, USA), with agreement assessed using Cohen's Kappa (κ: 99.4%). Any disagreements were resolved through consultation with a third author (N.K.).

Results

Identification of approved imaging tools

We identified four imaging techniques used for BCC assessment with approvals from both regulatory bodies (FDA and EMA), including dermoscopy, HFUS, OCT, and RCM. On the other hand, LC-OCT previously held only EMA approval but has now received 510(k) FDA clearance as of July 9, 2024. Table 1 provides a comprehensive overview of the fundamental principles of these modalities.

Selection of studies

Through a systematic search using the employed search terms across databases, a total of 2102 records were identified through database and register searching. The sources were drawn from Embase (850), Scopus (679), PubMed (545), and Cochrane (28). Additionally, 21 records were identified through manual citation searching. After identifying and removing 876 duplicates, 1247 unique records were screened. Among these records, 900 were eliminated as they did not align with the specified inclusion criteria outlined in Section 2.2. Following subsequent scoping assessments, the pool was refined to 347 full-text articles, which underwent a thorough evaluation, including full-text analysis. This process resulted in the exclusion of 336 articles that either met exclusion criteria or failed to meet inclusion criteria. A total of 11 studies met the specific scoping criteria and were included in this systematic scoping review (Figure 1).

Study characteristics

This systematic scoping review involved 11 studies published between 2007 and 2024, with funding sources disclosed in 27.3% of the studies.

The distribution of noninvasive skin imaging modalities includes OCT in 3 studies (27.3%), RCM in 3 studies (27.3%), dermoscopy in 2 studies (18.2%), HFUS in 2 studies (18.2%), and LC-OCT in 1 study (9.1%). The contributing countries are distributed as follows: Italy with 4 studies, the United States with 3 studies, China with 2 studies, and Romania and Germany with 1 study. Europe leads with 6 studies, followed by North America with 3 studies from the US, and Asia with 2 studies from China.[16,28–37]

Appendix 1 outlines the key attributes of the chosen studies.[16,28–37] In summary, the dermoscopy studies enrolled 307 lesions across two prospective clinical trials. HFUS investigations involved 150 lesions across two prospective clinical trials. OCT research encompassed 81 lesions distributed across two prospective observational studies and one clinical trial. The LC-OCT study included 63 lesions in one case–control study. RCM investigations involved 43 lesions across three studies,

Table 1 Comparison of different Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved skin imaging techniques, detailing their penetration depths, resolutions, imaging speeds, contrast sources, signal backgrounds, invasiveness, advantages and limitations

Imaging technique	Visualization depth	Resolution	Imaging speed	Source of contrast	Background of detected signal	Example devices
Dermoscopy[41–45]	Up to 100 μm	~10–30 μm	Real-time	Superficial penetrating visible light	Visual	• Heine DELTA 30[96] • Dermlite DL4[97] • Illuco IDS 1100[98]
HFUS[53–58]	1–10 mm	40–200 μm	Real-time	Tissue impedance differences	Reflection	• Vevo MD by VisualSonics[99] • DermaScan C by Cortex Technology[100] • Dermus SkinScanner[91]
OCT[63–67]	1–2 mm	1–15 μm	Real-time	Optical scattering properties	Reflectivity	• ZEISS® Cirrus HD-Oct[101] • SPECTRALIS® HRA + OCT[102]
LC-OCT[74,77–79]	500 μm	1–15 μm	Real-time	Optical scattering properties	Reflectivity	• DeepLive by Damae Medical[103]
RCM[88–90]	200–300 μm	~1 μm	Near real-time	Reflectivity	Cellular morphology	• Vivascope by Lucid Inc.[104] • Caliber I.D. (VivaScope)[105]

HFUS, high-frequency ultrasound; OCT, optical coherence tomography; LC-OCT, line-field confocal optical coherence tomography; RCM, reflectance confocal microscopy.

conducted as two prospective clinical trials and one observational study.

Diagnostic modalities in BCC margin assessment

Dermoscopy

In comparing the studies by Chen *et al.* and Caresana *et al.*, both focused on dermoscopy-guided surgical excision of BCC. Chen *et al.* implemented a 5 mm outward surgical margin based on dermoscopy-defined boundaries, with pathological assessments conducted at 2 mm intervals. Their findings revealed rates of complete excision with histopathologic negative margins at 95.8% for the 2 mm dermoscopy-guided tumor margin and 99.5% for the 4 mm dermoscopy-guided tumor margin, based on histopathologic evaluation using the bread loafing technique.[28] On the other hand, Caresana *et al.* employed an additional 2 mm surgical margin during excision, achieving a high 98.5% histologically confirmed complete removal of BCC based on standard histopathological processing. The concurrence between clinical and dermoscopic measurements was 65.5%, while in 34.5% of cases, dermoscopic evaluation indicated a larger peripheral extension than clinical examination.[29]

HFUS

Comparing the studies by Jambusaria-Pahlajani *et al.* and Desai *et al.*, both focused on HFUS for margin delineation in BCC. Jambusaria-Pahlajani *et al.* reported that 40 MHz HFUS, used for margin delineation, exhibited a sensitivity of 32% and a specificity of 88% compared to histopathology. The overall correct classification rate was 73%, highlighting the limitations of HFUS, particularly its low sensitivity in detecting tumor extension, especially in high-risk histological subtypes. The 40 MHz ultrasound exhibited a sensitivity of 33% (95% CI: 15–54) and a specificity of 81% (95% CI: 77–98) for tumors with a surface area of 1.74 cm2 or smaller, whereas tumors with a surface area greater than 1.74 cm^2 showed a sensitivity of 80% (95% CI: 23–83) and specificity of 84% (95% CI: 69–94), following an excision with a proposed surgical margin for the first stage of MMS, which averaged a 1- to 2-mm margin of clinically normal skin around the clinical margin of the tumor, with the section undergoing a full margin histological evaluation to correlate with HFUS-defined margins.[36] Conversely, Desai *et al.* focused on HFUS-aided margin delineation using a 20-MHz ultrasound, revealing histologically clear margins in 90% of cases. The width of each BCC was measured, and subsequently, they were excised with 4-mm margins; however, the histological evaluation technique was not specified.[16]

OCT

The studies by De Carvalho *et al.*, Alawi *et al.*, and Wang *et al.* collectively investigated the utility of OCT in guiding margin delineation for BCC skin lesions, substantiating their findings through histopathological validation. In the De Carvalho *et al.* study, BCC lesion margins were marked, maintaining a 2 mm safety distance. These marked margins underwent OCT scans at various positions to visualize tumor features, applying diagnostic criteria such as epidermal thickening and disruption of

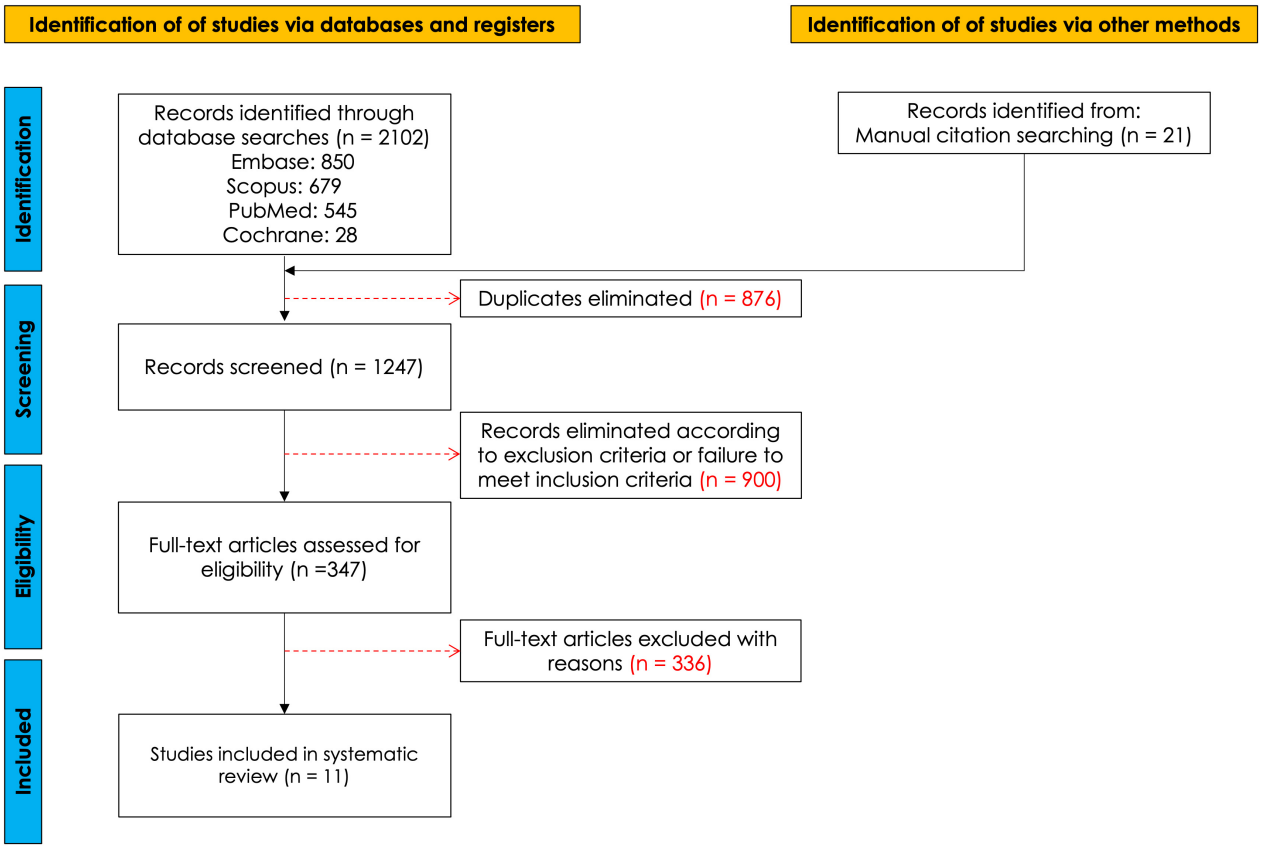

Figure 1 PRISMA flow diagram illustrating the screening and selection process conducted according to PRISMA-ScR guidelines. This diagram outlines the number of studies identified through database searches, the number of records screened, those excluded, and the final number of studies included in the review, as per the PRISMA-ScR framework for scoping reviews[27]

the dermal-epidermal junction. If OCT scans revealed features beyond the marked margin, it was extended by 2–3 mm. The outermost marked margin was selected for excision, and the excised tissue underwent a full-margin histological evaluation to correlate with OCT-defined margins. The OCT-guided margin delineation resulted in the complete excision of 8 out of 10 BCCs in a single stage and reduced the need for additional MMS stages in four patients.[30] In Alawi *et al.*'s study, OCT imaging was conducted on 18 patients with 19 lesions, including 12 cases of BCC, three squamous cell carcinomas, one Bowen's disease, one actinic keratosis, one seborrhoeic keratosis, and one poroma. High-resolution scans with a 6 × 6 mm dimension and up to 2 mm depth were performed using various scanning modes, including free-run and multislice, to visualize both lesions and healthy skin. The study aimed to delineate lesion margins using parallel and perpendicular scanning methods. Confirmed margins were marked with a waterproof pen for precise surgical excision guidance, followed by histopathology validation using the bread loafing technique. In this cohort of 18 patients encompassing 19 lesions, which included various skin lesions such as BCC and squamous cell carcinoma, OCT-guided margins demonstrated a remarkable accuracy, ensuring complete lesion removal in 84% of cases, while excisions based on marking the specific border were performed by different surgeons relying on their clinical experience. It is essential to note that the accuracy specifically for BCCs was not reported.[31] In the study by Wang *et al.*, a comprehensive examination was conducted on 52 biopsy-confirmed BCC lesions using MMS, involving a full-margin histopathological evaluation. OCT played a crucial role in this investigation, as a dermatologist marked estimated excision boundaries based on OCT images, which were then compared with histologically confirmed MMS excision points which were determined by a board-certified dermatologist trained and experienced in the performance of MMS. Results showed a 0% false-positive rate for lesional tissue detection and accurate margin prediction. Eleven of 52 lesions required a second MMS stage due to positive margins. In cases requiring a single MMS stage, OCT demonstrated a mean margin tightness of 0.4 ± 1.1 mm, aligning with the initial estimate. Moreover, OCT consistently placed the margin within the Mohs defect boundary, indicating a smaller lesion size by 1.4 ± 1.1 mm compared to Mohs excision. In instances

necessitating multiple MMS stages, OCT consistently anticipated lesion boundary extension beyond the planned Mohs defect boundary before excision.[32]

LC-OCT

Only one study was identified where the utility of LC-OCT in delineating BCC margins was studied. Paradisi *et al.*'s study focused on high-risk BCC patients undergoing MMS. The research included two groups: one assessed lateral margin using clinical, dermoscopic, and LC-OCT techniques, and a control group evaluated margins through clinical and dermoscopic means only. The study collected demographic and clinical data and performed MMS procedures with clinically and dermoscopically assessed safe distance of 2 mm from the lesion margin. It examined frozen sections to compare LC-OCT diagnoses with full-margin histopathological assessment, aiming to evaluate LC-OCT's effectiveness in defining tumor margins during surgery. LC-OCT was used to investigate central and peripheral BCC areas and guided the surgical process to ensure complete tumor removal while preserving healthy tissue. The study aimed to determine if LC-OCT could enhance the precision of lateral margin demarcation in high-risk BCC cases undergoing MMS. LC-OCT showed a significant difference in the mean number of MMS stages between the LC-OCT and control groups with dermoscopy alone (1.23 ± 0.43 SD and 1.89 ± 1.05 SD, respectively). LC-OCT's preoperative mapping of BCC tumor margins significantly reduced the patients' risk of undergoing >1 MMS stage compared to the control group in which dermoscopy was used to assess margins crude odds ratio: 0.3, 95% CI: 0.1–0.8.[37]

RCM

The studies by Pan *et al.*, Venturini *et al.*, and Lupu *et al.* investigated the utility of RCM in guiding margin delineation for BCC skin lesions. In Pan *et al.*'s study, the Vivascope 1500 (Caliber Imaging and Diagnostics, Rochester, NY, USA; Lucid Inc., Rochester, NY, USA; or Lucid Inc., MAVIG GmbH, Munich, Germany) RCM was used for mapping BCC borders. Thirteen patients with biopsy-confirmed BCC underwent surgical excision. The imaging protocol involved clinically evaluating and delineating the lesion border using a Wood's lamp and dermoscopy. Foci for RCM examination were selected within and outside this delineated border, identifying BCC features to establish an "RCM margin". An extra 5-mm margin of normal skin was excised, followed by an intraoperative frozen section biopsy to confirm surgical margins. The gross skin specimen was then sectioned along the boundaries identified by RCM and validated by intraoperative frozen section biopsy. The removed tissue underwent histopathologic analysis with standard histological examination, confirming the findings from the RCM. In all 13 cases where a 5 mm excision margin was employed, surgical margins were devoid of residual tumor.

Additionally, in 12 out of 13 cases (92.3%), frozen section results indicated negativity for a residual tumor at the RCM margins. The RCM margin was positive in a nodular-type BCC case, revealing cancer cells beneath the surface in one section.[33] Venturini *et al.* proposed a new approach combining dermoscopy and RCM for lateral margin detection in non-pigmented BCC with uncertain borders. They conducted margin-controlled surgical excision procedures, using dermoscopy to evaluate lesions presurgery and marking clear borders. For cases with unclear margins, superficial cuts were made. RCM was then used to visualize the lesion and superficial cuts, determining tumor-free or involved margins. All lesions were surgically excised based on RCM evaluation of the margins: lesions with an RCM-negative border were excised along the superficial cut (2 mm from identifiable tumor structures determined by dermoscopy and RCM), while lesions with an RCM-positive border were excised 4 mm from identifiable tumor structures. Tumor-free margins were removed along the superficial cut during surgical excision, and involved margins were excised 4 mm from identifiable tumor structures. Postsurgery, histopathological analysis with the bread loafing technique was employed to confirm the diagnosis and evaluate tumor presence concerning the superficial cut, aiming to enhance BCC removal precision by predefining tumor margins and minimizing the risk of residual cancerous cells. RCM identified BCC foci beyond the presurgical marker drawn by dermoscopic evaluation in 30% of lesions, with histological examination confirming the absence of BCC within 2 mm of the cut in 70% of cases.[34]

In Lupu *et al.*'s study, 18 patients with 20 suspected BCC lesions underwent a comprehensive dermoscopy and RCM evaluation. Dermoscopy was initially used to define lateral borders, followed by superficial incisions for marker stability. After achieving hemostasis, RCM images were captured to identify BCC characteristics. Dermoscopic lateral borders were initially drawn, and superficial incisions were made accordingly, positioned 2 mm away from any identifiable tumor structure determined through clinical examination. RCM assessment was then performed on each side of the incision to detect BCC criteria outside the incision or within 2 mm from the incision on the tumor side (termed a "positive" RCM margin) or the absence of such criteria (termed a "negative" RCM margin). Subsequently, lesions were surgically excised based on their RCM-defined lateral margins: "negative" RCM margin lesions were excised along the initial superficial incision, while "positive" RCM margin lesions had an additional 3 mm margin added. Histopathological examination confirmed BCC diagnosis and assessed tumor presence near the incisions. RCM examination did not detect BCC criteria extending beyond superficial incisions on the tumor side in any tumors, as confirmed by histopathology. However, within 2 mm from the superficial incision on the tumor side, RCM revealed BCC confocal criteria in four of the 29 evaluated margins. Histopathological examination showed tumor elements

in eight of the 29 evaluated margins on the tumor side of the incision. Therefore, with histopathological examination as the reference standard, RCM resulted in sensitivity and specificity for primary BCC lateral margin detection of 37.5% (95% CI: 8–75) and 95.2% (95% CI: 76–99), respectively.[35]

Discussion

Comparison of techniques

Dermoscopy enhances visualization of skin structures using polarized and non-polarized visible light and magnification, facilitating detailed examination of surface features not easily discernible with the naked eye.[38] Internal light sources in the dermoscope illuminate the skin, enhancing contrast and clarity: polarized light reduces surface glare, revealing deeper structures like blood vessels and pigmentation, while nonpolarized light assesses surface characteristics such as scales and texture.[39] Dermoscopes offer magnification levels from 10× to over 40×, meeting various diagnostic needs: 10× to 20× for a broad view, 20× to 40× for detailed examination, and over 40× for scrutinizing fine details within skin lesions.[40] It is routinely used in clinical practice to visualize skin microstructures, providing a resolution of ~10–30 μm and a depth of up to 100 μm.[41–45] In cases of BCC, dermoscopic features such as vascular patterns and specific pigmentary features aid in diagnosis, along with the absence of typical melanocytic features.[46–48] Applying these criteria ensures accurate BCC diagnoses, enhancing patient care. A cross-sectional survey of American Academy of Dermatology fellows found that approximately half utilized dermoscopy, with higher usage among younger practitioners, those teaching residents, or those with dermoscopy training.[49] Commercial dermoscopes range from 395 USD to around 1,795 USD.[50,51] Dermoscopy is approved by both the FDA and EMA.[25,26]

HFUS utilizes sound waves, typically ranging from 20 to 50 MHz or higher, to generate detailed images of internal structures, particularly in skin cancer imaging. A transducer on the skin permits sound wave penetration, revealing tissue density and composition through echo analysis.[52] With a resolution of 40–200 μm and a 1–10 mm penetration depth, HFUS offers real-time visualization of skin layers and lesion characteristics, aiding dermatologists in noninvasive assessment, diagnosis, and treatment planning for conditions such as skin cancer.[53–59] The frequency choice impacts imaging capabilities and system cost. Commercial HFUS scanners range from 6,000 USD for nonreal-time systems at 20 MHz to around 30,000 USD for real-time systems up to 50 MHz.[60] HFUS devices are approved by both the FDA and EMA.[25,26]

OCT, primarily used in ophthalmology, is a noninvasive imaging technique employing light waves to capture high-resolution cross-sectional images of biological tissues. It utilizes interferometry principles, splitting emitted light into reference and sample arms through a beam splitter, and creates an interferogram by interfering backscattered light from the sample arm with light from the reference arm.[61] Mathematical algorithms process the captured interferogram to generate depth-resolved A-scans, which combine to form cross-sectional B-scans or volumetric images. OCT provides real-time, high-resolution imaging crucial for tissue morphology understanding and medical decision-making in clinical practice,[61,62] offering detailed insights with micrometer-level precision, a resolution of 1–15 μm, and a penetration depth of 1–2 mm.[19,63–69]

OCT can detect birefringence, primarily from organized collagen fibers in the dermis, enabling the evaluation of basaloid islands crucial in diagnosing BCC.[21,70–72] Commercial OCT systems typically range from 40,000 USD to over 100,000 USD.[73] OCT has received approval from both the FDA and EMA.[25,26]

LC-OCT is a noninvasive imaging method utilizing a two-beam interference microscope with an 800 nm supercontinuum laser and a line-scan camera as a detector, emitting safe class 1 light onto the skin. It combines OCT interferometry with RCM's confocal spatial filtering to gauge the time of flight and amplitude of backscattered light from tissue microstructures illuminated by a line-shaped light. This provides three imaging modes (vertical, horizontal, and 3D stacks) with real-time production of vertical and horizontal sectional images at eight frames per second, reaching approximately 500 μm depth and a resolution of 1–15 μm.[74–79]

A standard research-grade LC-OCT system with supercontinuum light sources and camera technologies costs well over 100,000 USD.[80] The EMA has approved LC-OCT but not the FDA.[25,26]

RCM is an advanced optical imaging technique for real-time, noninvasive evaluation of skin lesions, offering high-resolution imaging of cytologic and architectural structures in the epidermis, dermo-epidermal junction, and upper dermis in horizontal scans.[81] It utilizes a focused laser beam to scan tissue, with reflected light collected by a confocal pinhole aperture to permit only in-focus light for the final image, eliminating out-of-focus light and improving optical sectioning and depth resolution.[82,83] RCM relies on differences in refractive indices and light scattering properties of cellular structures, leading to light reflectance variations, generating detailed, real-time images of cellular and tissue morphology without staining or invasive procedures, with a resolution of ~1 μm and a penetration depth of 200–300 μm. This noninvasive imaging modality has proven valuable in diagnosing early nonmelanoma skin cancers and melanomas, studying cellular dynamics, and aiding in assessing various diseases at a microscopic level.[84] RCM has received approval from both the FDA and EMA.[25,26] A clinical RCM device costs over 100,000 USD.[85]

Interpretation of results

Desai *et al.* explored HFUS-aided margin delineation using a 20-MHz ultrasound, achieving histologically clear margins in 90%, with excisions conducted with 4-mm margins.[16] In comparison, Chen *et al.* implemented dermoscopy-guided surgical margins,

reporting rates of complete excision with histopathologic negative margins at 95.8% for a 2 mm dermoscopy-guided tumor margin and 99.5% for a 4 mm dermoscopy-guided tumor margin.[28] While HFUS demonstrated promising results in achieving clear margins, the dermoscopy-guided approach showcased slightly higher rates of complete excision. However, further comparative studies are warranted to evaluate each technique's efficacy and potential advantages in clinical practice.

The use of RCM in guiding surgical excision for BCC demonstrated a sensitivity of 37.5% (95% CI: 8–75) but a high specificity of 95.2% (95% CI: 76–99) for primary lateral margin detection.[35] In comparison, HFUS exhibited high sensitivity in detecting tumor extension, with a reported sensitivity of 80% (95% CI: 23–83) and specificity of 84% (95% CI: 69–94) for tumors with a surface area greater than 1.74 cm^2.[36] However, a significant limitation of HFUS is its sensitivity drastically decreasing to 33% (95% CI: 15–54) and specificity 81% (95% CI: 77–98) for tumors with a surface area of 1.74 cm^2 or smaller.

LC-OCT, utilized in high-risk BCC patients undergoing MMS, exhibited a significant reduction in the mean number of MMS stages compared to the control group (1.23 ± 0.43 SD vs. 1.89 ± 1.05 SD). LC-OCT's preoperative mapping of BCC tumor margins also notably decreased the risk of >1 MMS stage (crude ORc: 0.3, 95% CI: 0.1–0.8).[37] Similarly, OCT-guided margin delineation demonstrated efficacy, with 8 out of 10 lesions excised in a single stage and minimized the need for additional MMS stages in patients. While both LC-OCT and OCT proved effective in optimizing surgical outcomes for BCC lesions, LC-OCT specifically targeted lateral margin demarcation, potentially reducing the number of surgical stages required and streamlining the overall surgical process, contrasting with OCT's focus on guiding excision boundaries.[30]

Using dermoscopy to guide surgical excision for BCC resulted in high rates of complete tumor removal with histopathologically negative margins, ranging from 95.8 to 99.5%, with surgical margins of 2 and 4 mm beyond the dermoscopy-determined tumor margin.[28] Discrepancies between clinical and dermoscopic measurements were observed in 34.5% of cases. Conversely, OCT showcased a histologically confirmed complete removal rate of 98.5% when employing an additional 2 mm surgical margin. In OCT-guided removal, margins were negative in 80 to 84%, with a 0% false-positive rate for lesional tissue during MMS, while excisions relying on marking the specific border were performed by different surgeons based on their clinical experience as the standard of care.[31] These findings suggest that OCT may not offer sufficient advantages to justify its cost and the time required for imaging compared to dermoscopy.

Synthesizing evidence

The published studies lack a uniform format, and most were performed on a few cases. Based on these limitations, comparing published findings on various imaging modalities for BCC margin assessment remains challenging. Mohs micrographic surgery shows a cure rate of over 99% with standard techniques for treating primary uncomplicated BCC, while excision is reported to be curative in 95% of cases.[86,87] These techniques regularly employ 2 and 4-mm margins. Although the possible advantages of the different imaging techniques are clear (Table 2), the current clinical evidence makes it hard to assess the potential real-world impact of imaging in BCC margin determination. Of all the techniques, dermoscopy stands out the most. Dermoscopy offers cost-effective initial examinations and timely intervention support with good sensitivity and specificity; therefore, dermoscopy can be an excellent addition to any dermatological surgeon's toolkit who does not already regularly assess BCC margins with dermoscopy. Dermoscopy also has considerable limitations; it lacks depth assessment and optical sectioning, making its utility less evident in high histological subtypes of BCC.[41–44] HFUS provides higher penetration depth and real-time visualization but suffers from operator dependency and lower resolution, impacting diagnostic reliability; however, it may provide invaluable information in large and thick BCCs.[53–58] OCT offers high-resolution imaging and depth information but requires expensive equipment and expertise, with a limited field of view and susceptibility to motion artifacts.[63–67] LC-OCT features parallel acquisition and high spatial resolution, reducing imaging time, but it has limited depth, higher complexity, and expertise requirements, and data on its utility for BCC margin determination is still limited.[74,77–79] RCM provides high-resolution cellular imaging with good sensitivity and specificity but has limited depth, operator-dependent interpretation, and higher equipment cost.[88–90]

Among these techniques, HFUS is particularly valuable for its high penetration depth, making it ideal for evaluating deeper or larger BCC lesions.[91] Conversely, RCM is considered the best for achieving high-resolution imaging, particularly for melanocytic lesions, as it provides detailed cellular-level information crucial for precise margin assessment.[88] Additionally, LC-OCT offers better penetration depth and convenient vertical imaging sections, with a resolution almost reaching that of RCM, making it a highly versatile technique.[92]

While effective, these modalities exhibit limitations. Dermoscopy lacks optical sectioning capabilities,[41–44] HFUS struggles to differentiate between deeper lesions and surrounding dermal layers,[93,94] and OCT is prone to motion artifacts.[63–67] LC-OCT setup complexities[74,77–79] and RCM's limited depth penetration pose challenges.[88–90] Maneuvering HFUS around certain anatomical sites adds practical difficulty.[93,95] These limitations, detailed in Table 2, highlight the potential of a multimodal approach to overcome constraints. Integrating various techniques may enhance BCC margin delineation and mitigate individual method limitations. The diverse techniques and methodologies and the lack of conclusive evidence from large, randomized trials hinder the clear determination of superiority. Most of the studies did not adhere to a standardized protocol. Due to the variability among study protocols, an objective

Table 2 Comparison of imaging modalities for skin lesion assessment: major advantages and limitations

Modality	Major advantage	Major limitation
Dermoscopy[41–44]	• Real-time assessment • Cost-effective initial examinations • Supports immediate evaluation for timely intervention • Good overall sensitivity and specificity • Low cost • Fast acquisition	• Limited depth assessment • Lack of optical sectioning capabilities • Accuracy may vary depending on the experience and expertise of the examiner, particularly if the physician does not interpret the specific dermoscopic finding, leading to lower sensitivity and specificity. • Potential for false positives/negatives
HFUS[53–58]	• Higher penetration depth • Real-time visualization • Operator adaptable for varied anatomical areas such as the face, scalp, trunk and extremities	• Operator skill impacts image quality • Lower resolution • Practical challenges in specific areas • Variability affecting diagnostic reliability • Limited soft tissue contrast
OCT[63–67]	• High-resolution cross-sectional imaging • Provides depth information • Real-time imaging capability • Versatile applications across medical fields	• Sensitive to tissue properties • Narrow field of view • Expensive equipment • Potential for artifacts, including motion artifacts• • Interpretation of OCT images requires expertise and training, potentially leading to variability in diagnosis among different operators.
LC-OCT[74,77–79]	• Parallel acquisition: Simultaneously captures entire lines of A-scans, reducing imaging time and minimizing motion artifacts. • Large field of view: Visualizes larger tissue areas in a single acquisition, facilitating comprehensive imaging without stitching. • High spatial resolution: Achieves detailed visualization of tissue microstructure and morphology, ideal for precise characterization. • Compatibility with multimodal imaging, including integration with reflectance confocal microscopy	• Limited imaging depth • Higher cost and complexity • Operator expertise needed • Practical challenges in specific areas • Complex data interpretation • Complexities in equipment setup, such as calibration requirements, alignment procedures, and configuration adjustments.
RCM[88–90]	• Offers high-resolution cellular imaging • High sensitivity and specificity for the diagnosis of various dermatoses	• Limited depth penetration • Operator-dependent interpretation • Restricted field of view • Higher equipment cost • Lack of standardized imaging protocols and interpretation criteria • Factors such as skin color, inflammation, or lesion location may hinder effective imaging with RCM.

HFUS, High-Frequency Ultrasound; OCT, Optical Coherence Tomography; LC-OCT, Line-Field Confocal Optical Coherence Tomography; RCM, Reflectance Confocal Microscopy.

comparative evaluation of these modalities is not feasible. Therefore, further research and comparative studies are essential to clarify efficacy and guide clinical practice effectively, and it would be crucial to carry out these studies with similar methodologies to allow for better comparability of results.

Conclusions

Imaging techniques such as dermoscopy, HFUS, OCT, LC-OCT, and RCM are rapidly advancing and hold significant potential to enhance the efficacy of MMS by improving the precision of BCC margin assessment, thereby reducing operation times and costs. Each modality offers distinct advantages: dermoscopy is cost-effective for initial assessments, HFUS is valuable for evaluating deeper lesions, OCT provides real-time depth information with high-resolution imaging, and LC-OCT facilitates multimodal imaging with parallel acquisition. LC-OCT is particularly useful for nonmelanocytic lesions due to its excellent resolution, improved penetration depth, and convenient vertical sectioning, making it a versatile tool in various clinical scenarios. Meanwhile, RCM is most useful for melanocytic lesions, enhancing diagnostic accuracy by providing cellular-level detail. Despite these advancements, the widespread adoption of these technologies in clinical practice will depend on their affordability and ease of use for dermatologists. As the prevalence of skin cancer continues to rise, integrating these imaging modalities into MMS could become crucial for optimizing patient outcomes. However, to establish the most effective imaging

protocols for BCC margin assessment, further well-designed, large-scale clinical studies are essential.

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Appendix 1

Primary features of the qualifying studies

Author	Year	Country	Non-invasive skin imaging tools	Patients (*n*)	Patient age	Patient gender	Lesions (*n*)	Design	Objective	Outcome
Chen *et al.*[28]	2022	China	Dermoscopy	107	Mean: 64.2 years Range: 42–84 years	Female: 38.3% Male: 61.7%	107	Prospective clinical trial	Evaluate dermoscopy's accuracy in defining BCC tumor margins for surgery by conducting pathological assessments at 2 mm intervals along the pre-marked direction with a 5 mm outward surgical margin based on the dermoscopy-defined boundary.	The rates of complete excision with histopathologic negative margins were 95.8% for the 2 mm dermoscopy-guided tumor margin and 99.5% for the 4 mm dermoscopy-guided tumor margin.
Caresana *et al.*[29]	2010	Italy	Dermoscopy	NR	NR	NR	200	Prospective clinical trial	Assess if dermoscopy improves BCC lateral border detection compared to clinical examination alone, aiming for over 95% radical excision with 2-mm margins.	Dermoscopy assessment and an additional 2 mm surgical margin during excision achieved 98.5% histologically confirmed complete removal of the BCC. Clinical and dermoscopic measurements showed 65.5% concurrence. In 34.5% (69 cases), dermoscopic evaluation indicated a greater peripheral extension than clinical assessment.
Jambusaria-pahlajani *et al.*[36]	2009	United States	HFUS	100	NR	NR	100	Prospective observational stu dy	Assess HFUS accuracy for tumor margin determination before Mohs surgery.	In margin detection, HFUS exhibited a sensitivity of 32% (95% CI: 15–54) and a specificity of 88% (95% CI: 78–94) compared to histopathology. This resulted in a positive predictive value of 47 and a negative predictive value of 79, with an overall correct classification rate of 73%. Understood
Desai *et al.*[16]	2007	United States	HFUS	NR	NR	NR	50	Prospective clinical trial	Evaluate HFUS for delineating BCC margins.	HFUS-aided margin delineation resulted in histologically clear margins in 90% of cases. However, 10% of BCCs showed extension beyond the 4-mm surgical margins and returned with positive margins.
De Carvalho *et al.*[30]	2018	Italy	OCT	10	Mean: 71.5 years Range: 52–82 years	Female: 50% Male: 50%	10	Prospective clinical trial	OCT to define BCC margins before MMS and reduce surgical stages.	OCT-guided margin delineation enabled the complete removal of eight out of ten BCCs in a single stage, minimizing additional MMS stages in four patients.
Alawi *et al.*[31]	2013	Germany	OCT	18	Mean: 74 Range: 47–86	Female: 66.7% Male: 33.3%	19	Prospective observational study	Assess OCT's viability in preoperative margin determination for skin lesions to evaluate the feasibility of different scanning techniques.	In 18 patients with 19 lesions, there were 12 cases of BCC, 3 cases of SCC, 1 case of Bowen disease, 1 case of AK, 1 case of seborrhoeic keratosis, and 1 case of poroma. OCT-guided margin determination ensured complete lesion removal in 84% of cases, affirming its role in reducing resection margins.

Appendix 1 Continued

Author	Year	Country	Non-invasive skin imaging tools	Patients (*n*)	Patient age	Patient gender	Lesions (*n*)	Design	Objective	Outcome
Wang *et al.*[32]	2013	United States	OCT	52	Mean: 65.2 Range: 38–85	Female: 50% Male: 50%	52	Prospective observational	Assess OCT's potential in defining surgical margins before Mohs surgery for BCC.	When comparing the initial clinical estimate and OCT predictions for lesion boundaries in cases requiring a single MMS stage, OCT consistently indicated the absolute lesion margin to be on or within the initial estimate, with a mean margin tightness of 0.4 ± 1.1 mm according to the OCT instrument. In cases requiring a single MMS procedure, OCT consistently placed the indicated margin within the Mohs defect boundary position, showing an average lesion size 1.4 ± 1.1 mm smaller than Mohs excision. In cases requiring multiple MMS stages, OCT predicted the extension of the lesion boundary beyond the planned Mohs defect boundary before excision in all instances.
Paradisi *et al.*[37]	2024	Italy	LC-OCT	60	Mean: 68.3 Range: 46–89	Male: 36.7% Female: 63.3%	63	Case–control	To investigate the effectiveness of preoperative LC-OCT evaluation in high-risk BCC margin assessment, aiming to reduce the number of MMS stages required for tumor clearance.	LC-OCT aided margin determination led to a significant reduction in the mean number of MMS stages compared to the control group, where only dermoscopy was used to define MMS margin (1.23 ± 0.43 SD and 1.89 ± 1.05 SD, respectively). LC-OCT preoperative mapping of BCC tumor margins significantly reduced the patient's risk of undergoing >1 MMS stage compared to the controls (crude odds ratio: 0.3 [95% CI 0.1–0.8])
Pan *et al.*[33]	2012	China	RCM	NR	NR	NR	13	Prospective clinical trial	Evaluation of RCM's feasibility in defining BCC margins presurgery.	With frozen section analysis, it was found that in 12 out of 13 cases, the clarity of the surgical margins, as identified by RCM, was supported by the biopsy results.
Venturini *et al.*[34]	2016	Italy	RCM	10	Mean: 68 years Range: 37–82 years	Female: 30% Male: 70%	10	Prospective clinical trial	Introduction of a novel method combining dermoscopy and RCM for nonpigmented BCC margin identification involves lesion examination with dermoscopy, delineation of clear borders 2 mm from identifiable structures using a dermographic pen, followed by a superficial dermoscopically guided cut before RCM examination to acquire mosaics up to 4 × 4 mm at various depths to assess tumor-free ('RCM-negative border') or involved margins ('RCM-positive border').	RCM identified BCC foci beyond the presurgical marker drawn by dermoscopic evaluation in 30% of lesions, with histological examination confirming the absence of BCC within 2 mm of the cut in 70% of cases. This approach revealed BCC foci beyond marked margins in three of ten lesions, confirmed by histology, improving margin identification for surgical excision in nonpigmented BCCs.

Appendix 1 Continued

Author	Year	Country	Non-invasive skin imaging tools	Patients (*n*)	Patient age	Patient gender	Lesions (*n*)	Design	Objective	Outcome
Lupu *et al.*[35]	2021	Romania	RCM	18	Mean 71.5 ± 6.35 years Range: 61–82 years	Female: 66.7% Male: 33.3%	20 (with 29 margins)	Prospective observational	Evaluate the preoperative accuracy of dermoscopy and RCM in determining BCC excision margins by drawing dermoscopic borders, creating superficial incisions as markers, utilizing confocal imaging to assess BCC features, and subsequently conducting histopathological examinations on surgically excised specimens.	A total of 29 borders were defined and marked by dermoscopic assessment. Of these, 21 showed no tumor presence according to histopathology, while the remaining 8 exhibited tumor elements. RCM assessment of the same 29 lesions within 2 mm of the superficial incision revealed 4 positive margins, with 3 aligning with histology to confirm tumor presence, and the histology of 1 margin indicating the tumor was farther away. Thus, RCM demonstrated 3 true positives, 1 false positive, 5 false negatives, and 21 true negatives, resulting in RCM sensitivity and specificity for primary BCC lateral margin detection of 37.5% (95% CI 8–75) and 95.2% (95% CI 76–99), respectively.

AK, actinic keratosis; BCC, basal cell carcinoma; CI, confidence interval; HFUS, high-frequency ultrasound; LC-OCT, line-field confocal optical coherence tomography; MMS, Mohs micrographic surgery; NR, not reported; OCT, optical coherence tomography; RCM, reflectance confocal microscopy; SCC, squamous cell carcinoma; SD, standard deviation.