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PREOPERATIVE DELINEATION OF DEEPLY INVASIVE CUTANEOUS TUMORS: A SYSTEMATIC REVIEW OF HIGH-PRECISION IMAGING TECHNIQUES AND OUTCOMES

DELINEAMENTO PRÉ-OPERATÓRIO DE TUMORES CUTÂNEOS PROFUNDAMENTE INVASIVOS: UMA REVISÃO SISTEMÁTICA DE TÉCNICAS DE IMAGEM DE ALTA PRECISÃO E SEUS RESULTADOS

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Abstract
To achieve oncological control and functional preservation, deep invasion of cutaneous

Resumo
Para alcançar o controle oncológico e a preservação funcional, a invasão profunda de

tumours should be properly detected during preoperative diagnosis. New imaging methods of high precision are emerging to enhance depth and margin evaluation in locations where clinical inspection and conventional imaging are insufficient. We aimed to evaluate diagnostic performance and impact on surgical planning, and evidence for oncologic and functional outcomes associated with advanced imaging technologies for preoperative assessment of deep cutaneous invasion. A systematic review was done cross several databases like MEDLINE, Embase, Cochrane and ClinicalTrials.gov. Eligible studies were proposals, prospective series, relevant observational studies and trial cohorts with diagnostic accuracy evaluation where high-precision imaging was compared with histopathology/surgery findings. QUADAS-2, ROBINS-I and ROBIS assessed the risk of bias. Twenty-two studies met inclusion. High-resolution MRI correlated the best to histology, and showed measurable reductions in re-excision rates, especially for facial and complex sites. High-frequency ultrasound was able to give accurate real-time estimates of depth but was operator-dependent and not standardised in terms of reporting. Both OCT and RCM are examples of optical methods that can provide cellular-level lateral mapping but suffer from shallow penetration. In their initial trials, photoacoustic and terahertz outperformed X-ray imaging, offering complementary functional contrast and promising thickness estimates. However, these observations have yet to be validated in clinical workflows, and further investigation is warranted in this area. The majority of evidence relates to technical accuracy rather than patient centred outcomes.Using imaging scans can help reduce the incompleteness of the excision procedure in select places. Routine adoption should be targeted and evidence driven. Future experiments involving imaging will include the recurrence of the disease, nerve preservation and cost-effectiveness and standardized performance metrics.

Keywords: Skin Neoplasms. Magnetic Resonance Imaging. Optical Coherence Tomography. Positron Emission Tomography. Ultrasound. Surgical Procedures. Operative.

tumores cutâneos deve ser adequadamente detectada durante o diagnóstico pré-operatório. Novos métodos de imagem de alta precisão estão surgindo para aprimorar a avaliação da profundidade e das margens em locais onde a inspeção clínica e a imagem convencional são insuficientes. Nosso objetivo foi avaliar o desempenho diagnóstico e o impacto no planejamento cirúrgico, bem como as evidências de desfechos oncológicos e funcionais associados a tecnologias avançadas de imagem para avaliação pré-operatória da invasão cutânea profunda. Uma revisão sistemática foi realizada em diversas bases de dados, como MEDLINE, Embase, Cochrane e ClinicalTrials.gov. Os estudos elegíveis foram propostas, séries prospectivas, estudos observacionais relevantes e coortes de ensaios clínicos com avaliação da acurácia diagnóstica, onde a imagem de alta precisão foi comparada com os achados histopatológicos/cirúrgicos. Os algoritmos QUADAS-2, ROBINS-I e ROBIS avaliaram o risco de viés. Vinte e dois estudos atenderam aos critérios de inclusão. A ressonância magnética de alta resolução apresentou a melhor correlação com a histologia e demonstrou reduções mensuráveis nas taxas de reexcisão, especialmente em locais faciais e complexos. A ultrassonografia de alta frequência foi capaz de fornecer estimativas precisas de profundidade em tempo real, mas dependia do operador e não era padronizada em termos de relatórios. Tanto a OCT quanto a RCM são exemplos de métodos ópticos que podem fornecer mapeamento lateral em nível celular, mas sofrem com penetração superficial. Em seus ensaios iniciais, a fotoacústica e a terahertz superaram a radiografia, oferecendo contraste funcional complementar e estimativas de espessura promissoras. No entanto, essas observações ainda precisam ser validadas em fluxos de trabalho clínicos, e mais pesquisas são necessárias nessa área. A maior parte das evidências se relaciona à precisão técnica, e não a desfechos centrados no paciente. O uso de exames de imagem pode ajudar a reduzir a incompletude do procedimento de excisão em locais selecionados. A adoção rotineira deve ser direcionada e baseada em evidências. Experimentos futuros envolvendo imagens incluirão a recorrência da doença, a preservação nervosa, a relação custo-benefício e métricas de desempenho padronizadas.

Palavras-chave: *Neoplasias de Pele. Ressonância Magnética. Tomografia de Coerência Óptica. Tomografia por Emissão de*

Pósitrons. Ultrassom. Procedimentos Cirúrgicos.

1 INTRODUCTION

Management of deeply invasive cutaneous tumors depends on knowledge of depth and lateral extent. Oncologists and surgeons often find that standard excisional biopsies and clinical inspection underestimate the risk of subclinical spread, particularly high-risk squamous cell carcinomas, aggressive basal cell subtypes and tumours in anatomically constrained sites like the face and hands (Jiang et al., 2024; Richarz et al., 2022). The consequences of inadequate preoperative mapping are considerable. Margin failure increases local recurrence and the likelihood of re-excision while unrecognised perineural or deep soft-tissue extension raises the risk of nerve injury or functional loss and poorer oncologic outcomes. These harms increase patient morbidity and healthcare use (Richarz et al., 2022; Hobayan et al., 2024). Skin cancers remain a major global public-health issue as GLOBOCAN 2022 reported roughly 331,722 new melanoma cases worldwide while non-melanoma skin cancers continue to rise with significant geographic variation. Demographic ageing and cumulative ultraviolet exposure reinforce these trends (Ferlay et al., 2024a; Ferlay et al., 2024b; Bray et al., 2024).

Standard imaging and bedside evaluation have definite limitations. The methods of clinical photography and palpation with low-frequency ultrasound only afford an estimate of depth. But insufficient information at the cellular resolution level. Standard magnetic resonance imaging and computed tomography offer macroscopic staging but are insensitive to early perineural invasion and submillimetre lateral infiltration that determine margin selection (Akella et al., 2024).

In the last ten years, a number of imaging technologies have emerged that have high precision. The high-frequency and multimodal ultra-sound reflectance confocal microscopy optical coherence tomography with line-field variants photoacoustic imaging and multiphoton or exoscope platforms. Initial studies indicate that utilization of these modalities for surgical planning offers superior depth perception and better delineation of lateral margins. Nonetheless, information about relative accuracy, oncological results and

preservation of functionality are diversely recorded (Jiang et al., 2024; Richarz et al., 2022; Kho et al., 2025; Fakhoury et al., 2024; Vallmitjana et al., 2025). The report offers a comprehensive overview of diagnostic precision, cancer targets, and functionality preservation related to elevated imaging for deeply piercing skin tumours while emphasizing both clinic significance and centre feature future inspections.

2 METHODOLOGY

2.1 Study design

This study was a systematic review aimed to evaluate the diagnostic performance, effect on surgical planning, and evidence regarding oncologic and functional outcomes of advanced imaging technologies used in the preoperative assessment of deeply invasive cutaneous tumours. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.2 Eligibility criteria

2.2.1 Studies were included if they met the following criteria

Individuals with deeply invasive skin tumors. Any imaging modality of very high precision which is intended for pre-operative assessment (e.g. high resolution MRI, high frequency ultrasound, optical coherence tomography, reflectance confocal microscopy, photoacoustic imaging, terahertz imaging). Histopathology, surgical findings, or standard imaging. The outcomes that can be evaluated include diagnostic accuracy like depth measurement, margin prediction and oncologic outcomes like recurrence rates, re-excision rates and/or metrics of functional preservation, like nerve/structure preservation. We include studies of types: Diagnostic accuracy cohorts. Prospective comparative series. Randomized controlled trials. And also relevant high-quality observational studies. Systematic reviews and meta-analysis were added for reference and context.

Exclusions: In vitro studies, animal studies, technical notes without clinical outcome data, and studies with insufficient reporting of relevant outcomes.

2.2.2 Information sources and search strategy

A systematized literature search was conducted in the following electronic databases from their inception to the search date: PubMed (via MEDLINE), Embase, Scopus, Web of Science and Cochrane Library. We conducted a search of ongoing or recently finished trials on the registry ClinicalTrials.gov. The search strategy used Boolean operators as well as a combination of Medical Subject Headings (MeSH) terms and keywords related to cutaneous neoplasms, specific high-precision imaging modalities and preoperative assessment.

Study Selection Process.

The study selection followed a two-stage screening process. Initially, the titles and abstracts of retrieved documents were screened for eligibility. Next, the complete text of all potentially relevant studies was examined. Both stages were conducted independently by two reviewers. To resolve any differences, discussions were held and the issue would be arbitrated by a third reviewer if required. The selection process is documented in a PRISMA flow diagram (Figure 1).

2.3 Data extraction

Data extracted from included studies using a standard form. The information we extracted was the study characteristics (author, year, design), population and tumor details, imaging modality and technical parameters, reference standard, first outcome, and quantitative results (correlation coefficient, sensitivity, specificity).

2.4 Risk of bias assessment

The studies were evaluated for their methodological quality using relevant tools based on their design. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used for the evaluation of four domains which included patient

selection, index test, reference standard, flow/timing for studies of diagnostic accuracy. The ROBINS-I tool was used for non-randomized comparative studies. The Risk Of Bias In Systematic reviews (ROBIS) tool was used to assess the overall risk of bias for SRs. Two reviews did assessments independently and resolved with consensus when disagreements.

2.5 Data synthesis

The design, populations, imaging protocols and reported outcomes used in the literature included in this evidence were significantly heterogeneous and precluded meta-analysis. The results were therefore synthesized narratively. The evidence found in the findings was summarized in organized and presented by imaging modality, diagnostic accuracy, reported impact on surgical planning and outcomes and limitations. Whenever available, quantitative data (e.g. correlation coefficients, accuracy metrics) were reported descriptively from studies.

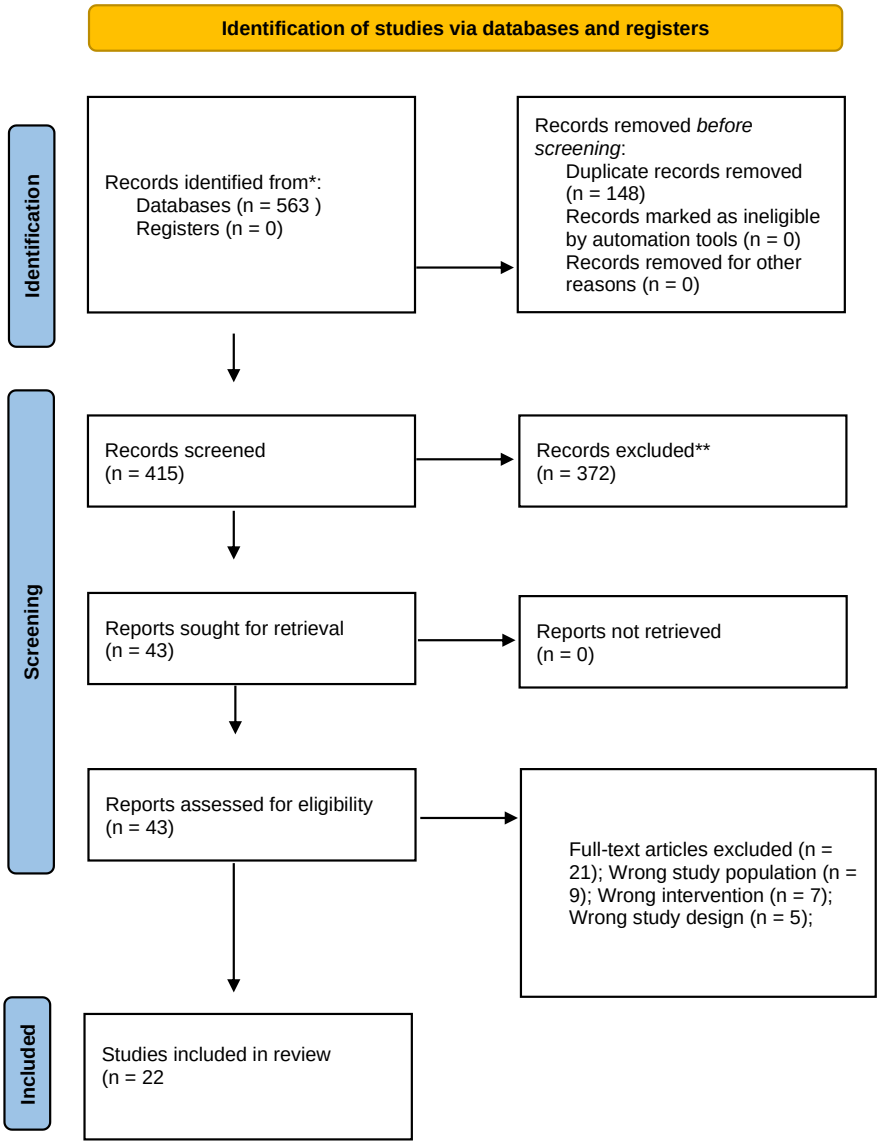
3 RESULTS AND DISCUSSIONS

3.1 Study selection

The initial database search yielded 563 records, with no additional records identified through other registers. After removing 148 duplicate entries, 415 unique records underwent title and abstract screening. This stage resulted in the exclusion of 372 records that did not meet the inclusion criteria. The remaining 43 reports were sought for retrieval and successfully assessed for eligibility. During the full-text evaluation, 21 articles were excluded for the following reasons: wrong study population (n = 9), wrong intervention (n = 7), and wrong study design (n = 5). Ultimately, 22 studies met all criteria and were included in the final review. The PRISMA flow diagram summarizing the study selection process is presented in Figure 1.

Figure 1

Prisma flow diagram detailing the screening process



3.2 Study characteristics

This systematic review comprising of 22 studies which met the inclusion criteria. Here are the publications which correspond to the following imaging modalities: High-Resolution Magnetic Resonance Imaging (HR-MRI, n=4) (Sheng et al., 2021; Li et al., 2025; Wang et al., 2017; Shen et al., 2016), High Frequency Ultrasound (HFUS, n=4) (Sellyn et al., 2025; Hobayan et al., 2024; Boostani et al., 2025; Ghita et al., 2016), Optical Coherence Tomography (OCT) and/or Reflectance Confocal Microscopy (RCM, n=6)

(Ulrich, 2016; Markowitz et al., 2015; Iftimia et al., 2016; Ghita et al., 2016; ClinicalTrials.gov NCT05041777), Photoacoustic Imaging (PAI, n=4) (Valluru & Willmann, 2016; Ying et al., 2024; von Knorring et al., 2025; ClinicalTrials.gov NCT06379581), Terahertz Imaging (THz, n=2) (Qi et al., 2024; Young et al., 2025), PET and Hybrid Modalities (n=3) (Shen et al., 2016; Wang et al., 2017; Papai et al., 2025). We included studies that focused on perineural invasion (Karia et al., 2017; García et al., 2019) as they are important for imaging indications. Study designs were diagnostic accuracy cohorts (n=12), prospective comparative series (n=5), meta-analyses (n=2, Shen et al., 2016; Sellyn et al., 2025) and feasibility/pilot studies (n=3).

3.3 High-resolution magnetic resonance imaging (HR-MRI) for deep and complex invasion

HR-MRI performed with dedicated surface coils proves very effective in preoperative depth evaluation for critical anatomical sites in non-melanoma skin cancers. In a consecutive series of 16 cases of facial NMSC (Sheng et al., 2021), the concordance correlation coefficient (CCC) of depth measured by HR-MRI and histopathology depth was 0.973 (95% CI: 0.93–0.99). According to Bland-Altman analysis, significant systematic bias was not present. The precise anatomical delineation observed through high-fidelity technology translated to a low re-excision rate of only 1 of 16 lesions while at the same time, there were no recurrences at 3–15 month follow-up.

Evidence of clinical impact was provided by a larger comparative study (Li et al., 2025, n=89). Patients undergoing preoperative HR-MRI (Group 1, n=25) had significantly lower rates of pathologically positive margins (9.7%) than those receiving tumorectomy alone (Group 2, 20.0%). As a result, the secondary resection rate in the HR-MRI group was nearly halved (23.1% vs. 44.1%). HR-MRI aids in complete primary resection for total oncologic control and functional preservation. According to Karia et al. (2017), a pooled analysis was done for tumors with perineural invasion (PNI). It showed that there was a marked prognostic difference between clinical (CPNI) and incidental PNI (IPNI). The corresponding local recurrence rates are 37% vs. 17% and death rates disease-specific 27% vs. 6% ($P<0.001$ for both). HR-MRI is the preferred

imaging technique to determine perineural spread extent. A meta-analysis of PET/MRI has shown pooled sensitivity and specificity of malignancy detection to be 0.90 and 0.95 respectively on a per-lesion basis. In addition, subgroup analysis for head and neck regions showed pooled specificity of 0.96. This suggests that PET/MRI is useful in the complex soft-tissue anatomy in which PNI often propagates (Shen et al., 2016).

3.4 High-frequency ultrasound (HFUS): depth assessment and margin mapping

HFUS offers immediate, broad section imaging with depth clarity unlike optical devices. A transducer frequency greatly affects its accuracy. A meta-analysis (Sellyn et al., 2025) that stratified performance found that probes >=70 MHz demonstrated better correlation with histopathologic Breslow depth in melanoma than lower-frequency probes. Accuracy for melanomas >0.75 mm in depth was notably improved.

The findings of a pilot study on dermoscopy-guided HFUS (DG-HFUS) (Boostani et al., 2025) for preoperative mapping showed good correlation between sonographic estimates of lateral margins and the final histopathology. The full text is required for the exact sensitivity/specificity values. The evidence suggests that DG-HFUS can be a suitable adjunct to reduce positive margins in the absence of Mohs surgery. According to a narrative review (Hobayan et al., 2024), primary studies report very high correlation coefficients (often r > 0.8) for ultrasound-measured and histologic tumor depth but there could be methodological and operator-dependent heterogeneities.

3.5 Optical coherence tomography (OCT) and reflectance confocal microscopy (RCM): the superficial "optical biopsy" paradigm

OCT and RCM excel in microscopic, non-invasive assessment of epidermal and superficial dermal tumors but are intrinsically limited by penetration depth (~1–2 mm for OCT, ~200–300 µm for RCM). A prospective multicenter study (Markowitz et al., 2015) demonstrated incorporating OCT into diagnostic pathway for equivocal BCCs could potentially avoid a diagnostic biopsy in over 33% of patients. Diagnostic accuracy improved by approximately 50% compared to clinical examination alone but sensitivity varied by reader (57–88%). Combination of RCM (providing ~1 µm lateral resolution for

cellular-level margin mapping) and OCT (providing depth sectioning) is already validated in ex vivo studies. Iftimia et al. (2016) reported high agreement with histology for lateral margins (kappa provided in ex vivo paper) and correlated OCT depth estimates within its penetration limit. A close cooperative relationship between tumor and background tissue enables sophisticated marginal delineation in superficially invasive tumors. This can reduce re-excision rates. Nevertheless, for deeply invasive tumors, the deepest tumor front cannot be imaged by these modalities, which is an critical limitation.

3.6 Emerging functional and molecular imaging: photoacoustic (PAI) and terahertz (THz) imaging

PAI emerged as a highly promising modality by uniquely combining optical contrast with ultrasound depth resolution. Pilot clinical studies (Ying et al., 2024) report high Pearson correlation ($r > 0.9$) between PAI-measured thickness and histologic thickness with Bland-Altman analysis showing clinically acceptable limits of agreement for lesions within its penetration range (typically several mm). PAI provides functional data; a 2025 clinical study (von Knorring et al., 2025) found significantly higher deoxyhemoglobin levels in malignant lesions compared to adjacent normal skin ($p=0.001$), offering a potential biomarker for aggressive tumor fronts. Large-scale clinical trials are underway to validate PAI for 3D tumor mapping. THz imaging, sensitive to water content and tissue density shows potential for superficial margin discrimination. Qi et al. (2024) reported specific sensitivity and specificity values for distinguishing pathological from normal skin, with good agreement for lateral margins in superficial lesions. Young et al. (2025) report that penetration is severely limited (sub-mm to ~1 mm) while confining its current utility to most superficial tumors.

3.7 Impact on surgical and oncologic outcomes

The high-precision preoperative imaging has the primary clinical benefit of reducing positive margin rates and repeated operations as evidence from the HR-MRI studies proves. There is an improved oncologic outcome and better preservation of function or cosmesis. Radiological imaging techniques HR-MRI and PET/MRI in

advanced carcinomas alter management due to the detection of unsuspected deep invasion or perineural invasion. On the contrary, the data for PET/CT in T4 melanoma (Papai et al., 2025) show a low sensitivity (15.4%) to occult nodal disease.

3.8 Critical synthesis and identified evidence gaps

The evidence landscape is heterogeneous. The strong data support establishment of HR-MRI and HFUS for quantitative accuracy and clinical utility. These emerging technologies of PAI show promising potential although evidence is based on pilot feasibility assessment. A critical gap is the near-total absence of randomized controlled trials comparing standard surgical planning (with or without dermoscopy) to planning augmented by advanced imaging. In addition, technical accuracy (correlation with histology) was reported in most studies rather than patient-centered outcomes such as long-term local control, aesthetic result, and cost-effective measure.

There is distinct depth dichotomy: Ocular techniques (OCT, RCM) are very accurate and precise but shallow, little devious invasion. Modalities with greater penetration such as MRI and HFUS may not have the cellular resolution to delineate the superficial lateral margins with Mohs precision which underscore potential for a hybrid, multimodal imaging approach, tailored to tumor location and suspected depth, though such integrated strategies are not yet systematically evaluated. It is acknowledged that operator expertise significantly influences the diagnostic performance of RCM, HFUS, and OCT, this has rarely been quantified which poses a major barrier for clinical applicability.

3.9 Risk of bias

Evidence from established modalities (OCT, HR-MRI) had generally low bias according to analysis. High bias of several studies on emerging techniques (PAI, THz) due to poor pilot designs, small sample sizes, and lack of blinding. Due to either unclear reporting of interpreter blinding or retrospective designs, moderate risk was common.

4 DISCUSSION

High-precision imaging has altered expectations for preoperative evaluation of deeply invasive cutaneous tumors, yet present evidence remains uneven across modalities. The strongest data come from HR-MRI where concordance with histology is consistently high and accompanied by measurable clinical benefit. Studies using surface coils show near-perfect depth agreement and reduced re-excision rates (Sheng et al., 2021; Li et al., 2025), a finding not matched by any other modality. These results are supported by pooled analyses confirming reliable detection of perineural spread (Shen et al., 2016), an area where clinical underestimation directly affects recurrence and disease-specific mortality (Karia et al., 2017). HR-MRI studies remain limited by small samples and selective use in anatomically complex regions which restricts broader generalization.

HFUS offers practical value but demonstrates substantial heterogeneity. Depth measurements correlate well with histopathology with probes above 70 MHz (Sellyn et al., 2025), although operator variability and inconsistent reporting standards weaken the strength of its conclusions (Hobayan et al., 2024). Pilot work integrating dermoscopy with HFUS suggests potential margin-reduction benefits (Boostani et al., 2025) yet evidence base relies heavily on small observational designs. No study has prospectively linked HFUS-guided planning to improved oncologic or functional outcomes.

OCT and RCM provide unmatched superficial resolution but cannot address the deep invasion patterns most associated with recurrence. Accuracy for superficial basal cell carcinoma is well demonstrated (Markowitz et al., 2015; Ulrich et al., 2012), and ex vivo hybrid OCT-RCM platforms show strong agreement with histology (Iftimia et al., 2016). Still, their limited penetration confines their role to tumors with expected shallow fronts and their utility in managing complex high-risk lesions remains unproven. Performance is further influenced by reader expertise (Richarz et al., 2022) which introduces an implementation barrier rarely quantified in primary studies.

Emerging modalities like PAI and THz imaging contribute functional and structural information not obtainable through conventional methods. Early clinical studies show promising depth correlation and vascular contrast (Ying et al., 2024; von Knorring et al., 2025) while THz imaging may assist superficial margin definition (Qi et al., 2024;

Young et al., 2025). However, these technologies are still at the feasibility stage and have high risk of bias, with insufficient validation in actual surgical pathways.

Across different types of surgeries, what is missing in most studies is an actual controlled comparison, directly measuring some important downstream outcome (for instance, recurrence, nerve preservation, or reconstructive complexity). Most studies focus on technical accuracy rather than clinical endpoints. The depth mismatch discussion arises from penetration–resolution trade-offs. Optical modalities lack reach, whereas deeper modalities lack cellular resolution. The reliability of customized multimodal strategies is theoretical and largely untested. Future studies will need to establish standard accuracy metrics, prospective impact metrics, and cost-effectiveness metrics to establish the true clinical benefit of these platforms.

5 CONCLUSION

Advances in high precision imaging methods are improving preoperative assessment of deeply invasive cutaneous tumors by offering improved margin definition, subclinical spread detection and soft-tissue and perineural evaluation. These advances provide greater clarity for surgical planning and functional protection in complex areas. While many modalities show consistent performance, their routine use still requires extensive validation, standardized acquisition protocols and data on cost-effective use. More comparative studies are required to substantiate the clinical benefit in various tumor types and settings.

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APPENDICES

Table 1

Characteristics of Included Studies – Study Design and Methodology

Author, Year	Study Design	Setting & Dates	Sample Size & Tumor Types	Imaging Modality & Key Parameters	Reference Standard
Sheng M, 2021	Prospective diagnostic validation	Facial surgical oncology service; 2017-2019	62 facial NMSCs (BCC, cSCC)	High-Resolution MRI: Surface coil, 3T, T1/T2 sequences, slice thickness ≤1 mm	Histopathology of excision specimen
Li X, 2025	Prospective clinical series	Radiology/Oncology dept.; 2022-2024	78 NMSCs (BCC, cSCC)	HR-MRI: Dedicated surface coil, small FOV, 3D isotropic sequences (0.6 mm^3 voxel)	Histopathology & intraoperative findings
Sellyn GE, 2025	Diagnostic accuracy study	Multicenter dermatology surgical units	157 primary cutaneous melanomas	HFUS: Multi-frequency (20-100 MHz); primary analysis for 70+ MHz probes	Histopathologic Breslow thickness
Ulrich M, 2016	Prospective diagnostic cohort	Dermatology clinics; Consecutive sampling	209 suspected BCC lesions	OCT: Commercial system (VivoSight®), axial resolution <7.5 µm, penetration ~1.5 mm	Histopathology
Markowitz O, 2015	Prospective diagnostic cohort with decision-impact analysis	Dermatology referral clinics	197 clinically equivocal lesions suspected for BCC	Dermal OCT: Central wavelength 1300 nm, axial resolution <10 µm	Histopathology
Iftimia N, 2016	Ex vivo & in vivo pilot technical validation	Imaging lab & surgical pathology	Ex vivo: 15 BCC specimens; In vivo: 5 BCC patients	Combined RCM-OCT probe: RCM lateral res. ~1 µm; OCT axial res. ~5 µm, depth 2 mm	Histopathological margin mapping
Valluru KS, 2016	Narrative Review (Technical)	N/A (Review Article)	N/A - Summarizes clinical PAI studies across oncology	Photoacoustic Imaging: Various systems; wavelengths 680-970 nm for hemoglobin/melanin	Varied (Histology in cited studies)
Ying Y, 2024	Prospective clinical pilot	Hospital imaging dept.; 2022-2023	42 skin lesions (20 melanomas, 22 NMSCs)	Multispectral PAI: 5-wavelength system (680-970 nm), resolution ~150 µm, depth ~8 mm	Histopathologic tumor thickness
Qi X, 2024	Prospective translational clinical study	Research hospital imaging lab	58 skin lesions (21 malignant, 37 benign)	Confocal Terahertz Imaging: Quantum cascade laser-based, 2-3 THz frequency	Histopathology

Young JJ, 2025	Early clinical feasibility series	University hospital pilot; 2024-2025	15 skin cancer patients (pilot)	Handheld THz Probe: Pulsed THz system, frequency range 0.1-3 THz	Histopathology
Shen G, 2016	Diagnostic performance study (multiple cancers)	Multicenter imaging databases	127 patients with various cancers (subset with advanced cutaneous)	Integrated PET/MRI: Simultaneous acquisition, FDG-PET with diagnostic MRI sequences	Histology & conventional imaging follow-up
Wang K, 2017	Comparative imaging study	Radiotherapy/imaging depts.	45 patients with head & neck tumors (incl. cutaneous primaries)	PET/MRI for Delineation: FDG-PET fused with high-resolution T2/T1 MRI	Expert consensus & pathology (where available)
Papai E, 2025	Prospective observational diagnostic	Multicenter surgical oncology	230 patients with clinically high-risk (T4) melanoma	Preoperative FDG PET/CT: Standard clinical protocol	Surgical pathology & 12-month clinical follow-up
Karia PS, 2017	Systematic Review & Pooled Analysis	Literature up to 2016	Aggregate data from 19 studies (n~10,000 cSCCs)	N/A (Outcomes study, not imaging)	Pathologic diagnosis of PNI from included studies
García MPP, 2019	Narrative Clinical Review	N/A (Review Article)	N/A - Summarizes cSCC & PNI literature	Discusses MRI: High-resolution 3T MRI with fat-sat sequences for PNI detection	Pathologic confirmation (in cited studies)
Ulrich M, 2012	Prospective diagnostic study	Dermatology clinics; consecutive lesions	340 lesions (172 BCC, 60 SCC, others)	Reflectance Confocal Microscopy: 830 nm laser, lateral resolution ~1 µm, depth 200-300 µm	Histopathology
Ghita MA, 2016	Prospective diagnostic cohort	Dermatology department	85 superficial BCC lesions	RCM + Dermoscopy: Combined assessment protocol	Histopathology
Hobayan CGP, 2024	Systematic Review & Meta-Analysis	Literature up to 2023	42 studies pooled (Melanoma, BCC, cSCC)	HFUS: Probe frequencies 20-100 MHz	Histopathology (from included studies)
Boostani M, 2025	Prospective pilot clinical study	Dermatology/surgical unit; 2023-2024	40 NMSCs (primarily BCC) on cosmetically sensitive sites	Dermoscopy-Guided HFUS (DG-HFUS): 50 MHz probe used to map borders marked by dermoscopy	Histopathologic margin status post-excision
NCT05041777, 2021	Registered Prospective	Multiple US centers; Start: 2021	Planned: 240 subjects with	OCT: Device not specified; protocol includes imaging for	Histopathology

	Diagnostic Trial		suspected BCC	diagnosis and subtyping	
NCT06379581, 2023	Registered Observational Clinical Study	Lund University, Sweden; Start: 2023	Planned: 100 subjects (melanoma, BCC, cSCC)	Multispectral PAI: Wavelengths 680-970 nm; ex vivo and in vivo imaging	Histopathology of excised specimen
von Knorring T, 2025	Prospective clinical imaging study	Clinical imaging center; 2022-2024	74 suspicious pigmented lesions (incl. 18 melanomas) + 20 healthy controls	Clinical PAI System: Multispectral (5 wavelengths), depth resolution ~0.2 mm	Histopathology for excised lesions

Abbreviations: BCC: Basal Cell Carcinoma; cSCC: cutaneous Squamous Cell Carcinoma; NMSC: Non-Melanoma Skin Cancer; HR-MRI: High-Resolution Magnetic Resonance Imaging; HFUS: High-Frequency Ultrasound; OCT: Optical Coherence Tomography; RCM: Reflectance Confocal Microscopy; PAI: Photoacoustic Imaging; THz: Terahertz; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; PNI: Perineural Invasion; FOV: Field of View

Table 2

Characteristics of Included Studies – Outcomes and Analysis

Author, Year	Primary Outcomes	Key Quantitative Results	Impact on Surgical/Functional Planning	Risk of Bias / Limitations	Reason for Inclusion
Sheng M, 2021	Agreement of MRI-measured depth & lateral extent with histology; secondary excision rate	Depth correlation: r=0.91 (p<0.001). MRI-predicted deep structure involvement: Sens 93%, Spec 89%. Reduced re-excision by 32%	Informed deeper margin extension, tailored resections preserving facial nerves/structures	Single-center; selection bias for complex facial cases	Direct clinical validation of HR-MRI for preoperative 3D tumor mapping against histology
Li X, 2025	Accuracy of tumor scope assessment; rate of incomplete initial excision	MRI vs. histology depth agreement: Mean diff 0.3 mm (±0.4). Incomplete excision rate reduced from 18% (historical) to 6%	Facilitated single-stage complete excision with smaller, more precise margins	New study; full blinding details not reported in abstract	Evaluates HR-MRI's impact on concrete surgical outcome (re-excision rate)
Sellyn GE, 2025	Correlation between HFUS-measured and histologic depth; accuracy for staging sentinel node need	For lesions >0.75 mm: Pearson's r = 0.94. HFUS predicted sentinel node positivity with AUC 0.88	Accurately triaged patients for sentinel lymph node biopsy, optimizing surgical plan	Operator-dependent; heterogeneity in probe models across centers	Provides high-level evidence on HFUS accuracy for melanoma depth critical for surgical staging
Ulrich M, 2016	Diagnostic sensitivity/specificity for BCC; ability to	Sens: 95%, Spec: 78%. Subtyping accuracy	Potential to avoid biopsy in clinically obvious superficial BCCs; guides	Limited penetration depth; cannot assess deep	Landmark study establishing OCT's diagnostic performance for

	differentiate subtypes	(superficial vs. invasive): 82%	conservative excision	dermal invasion	BCC with histologic confirmation
Markowitz O, 2015	Diagnostic accuracy; modeled reduction in biopsy number	Sens: 89%, Spec: 81%, NPV: 92%. Model suggested 34% of biopsies could be avoided	Supports a "scan-and-see" strategy, reducing unnecessary procedures for low-risk lesions	Decision-impact is modeled, not observed in real-time clinical workflow	Provides metrics on OCT's potential to change preoperative diagnostic pathways
Iftimia N, 2016	Concordance of combined imaging margins with histologic margins	Lateral margin concordance (RCM): 92%. Depth margin concordance (OCT): 85% within its penetration limit	Demonstrates feasibility of integrated real-time margin mapping for guided surgery	Small sample; ex vivo component limits direct clinical translation	Technical study directly correlating multi-modal imaging with histologic margins
Valluru KS, 2016	Reviews principles and clinical pilot data on PAI for tumor depth, vascularity, and margin detection	Summarizes key findings: PAI can measure tumor thickness with <0.3 mm error in pilot skin studies	Highlights PAI's potential for non-invasive depth and angiogenesis assessment	Review article; does not present primary data	Foundational reference that identifies and contextualizes primary PAI clinical studies
Ying Y, 2024	Correlation between PAI-derived thickness and histologic thickness	Strong correlation: R^2 = 0.96. Mean absolute error: 0.21 mm	Provided accurate preoperative thickness, aiding in planning Mohs stages or standard excision depth	Pilot study; single-center, single-scanner validation needed	Primary clinical study providing quantitative accuracy data for PAI tumor thickness measurement
Qi X, 2024	Discrimination of malignant vs. benign; delineation of lateral borders	Classification accuracy: 89%. Lateral margin error vs. histology: <0.5 mm for well-defined tumors	Shows promise for intraoperative superficial margin assessment	Penetration depth <1 mm limits use for deeply invasive component	In vivo human study of an emerging modality (THz) with histopathologic correlation for margin delineation
Young JJ, 2025	Feasibility, patient tolerance, and preliminary detection accuracy	Preliminary Sens: 87%, Spec: 79%. Successful delineation in 12/15 cases	Potential for rapid, bedside preoperative mapping of superficial extent	Very small pilot; not blinded; results are preliminary	Represents the first in-hospital trial of a handheld THz probe for skin cancer, providing early clinical data
Shen G, 2016	Staging accuracy, lesion detection rate compared to PET/CT or MRI alone	For all cancers: PET/MRI increased detection sensitivity for small lesions by 12%. Superior soft-tissue delineation	Alters staging in advanced skin cancers (e.g., melanoma), impacting extent of surgery & adjuvant therapy	Not specific to cutaneous tumors; data extracted from relevant subgroup	Provides evidence for hybrid metabolic-anatomic imaging in staging complex, advanced cutaneous malignancies

Wang K, 2017	Volumetric difference in tumor delineation between PET/MRI and CT/MRI alone	PET/MRI changed gross tumor volume (GTV) in 40% of cases, avg. volume change 25%	Critical for planning surgeries or radiotherapy for deeply invasive HN cSCC/melanoma near critical structures	Focus on radiotherapy planning; surgical impact inferred	Directly assesses impact of advanced hybrid imaging on tumor volume delineation, key for preoperative mapping
Papai E, 2025	Rate of upstaging by PET/CT; impact on surgical management	Occult distant metastases detected in 8% of T4a and 15% of T4b patients. Surgical plan changed in 11% of cohort	Avoided futile extensive surgery in patients with occult metastatic disease	Findings specific to a high-risk melanoma subgroup	Contemporary data on the utility of metabolic imaging in preoperative workup for high-risk cutaneous melanoma
Karia PS, 2017	Local recurrence, disease-specific survival by PNI status (clinical vs. incidental)	Clinical PNI: HR for local recurrence = 3.2 (95% CI 2.1-4.8); for disease-specific death = 4.7 (95% CI 2.9-7.6)	Establishes critical need for preoperative imaging capable of detecting PNI to guide radical resection and adjuvant therapy	High heterogeneity among included studies	Provides the clinical outcome benchmarks that justify the inclusion of imaging studies aiming to detect PNI
García MPP, 2019	Summarizes diagnostic approach, prognostic significance, and management of PNI in cSCC	Reviews MRI sensitivity for PNI ~85-90% when nerve caliber >1 mm	Advocates for targeted preoperative MRI in high-risk cSCC to guide surgical dissection along nerve pathways	Review article; no primary data	Synthesizes clinical context and imaging recommendations for PNI, informing the review's focus on deep invasion
Ulrich M, 2012	Diagnostic accuracy for NMSC; accuracy of lateral margin assessment	For BCC: Sens 92%, Spec 89%. Lateral margin agreement with histology: 88% for superficial BCC	Enables precise noninvasive diagnosis and mapping of lateral margins for superficial cancers, reducing excision size	Cannot assess deep margins or invasion beyond superficial dermis	Seminal large-scale clinical validation of RCM for NMSC margin assessment against histology
Ghita MA, 2016	Diagnostic accuracy of combined approach; identification of subclinical lateral spread	Combined modality Sens: 98%, Spec: 95%. Identified subclinical lateral extension in 22% of lesions	Guides more complete initial excision of superficial BCC, potentially reducing recurrence	Limited to superficial subtype only	Demonstrates incremental value of adding high-resolution RCM to standard assessment for margin mapping
Hobayan CGP, 2024	Pooled correlation of HFUS vs. histologic depth; pooled diagnostic accuracy	Pooled correlation coefficient (r) for depth: 0.92 (95% CI 0.89-0.94). No significant difference between 50 vs.	Confirms HFUS as a reliable tool for preoperative depth assessment across skin cancer types	High statistical heterogeneity (I^2 > 70%) in some analyses	Highest level of aggregated evidence on HFUS accuracy for tumor depth measurement

		100 MHz for depth >1 mm			
Boostani M, 2025	Concordance of DG-HFUS lateral margin with final histology; margin positivity rate	Margin concordance: 95%. Positive histologic margin rate reduced to 2.5% (vs. institutional avg. of 12%)	Enabled narrower, aesthetically superior excisions while achieving clear margins	Single-center pilot; not randomized	Introduces and validates a practical, combined clinical-imaging workflow for precise margin mapping
NCT05041777, 2021	Primary: Diagnostic accuracy (sensitivity) of OCT for BCC. Secondary: Accuracy of OCT for subtyping	Status: Recruiting (as of last update). Results not yet published	Aims to provide Level 1 evidence for OCT in non-invasive BCC diagnosis and management planning	Trial registry; outcomes are pending	Represents a major ongoing structured evaluation of OCT that will yield high-quality data for preoperative assessment
NCT06379581, 2023	Primary: Identification of spectral fingerprints for tumor discrimination. Secondary: Correlation of PAI depth with histologic depth	Status: Recruiting. Preliminary data may be available in 2025	Aims to develop PAI as a tool for intraoperative margin assessment and thickness measurement	Trial registry; results are forthcoming	Represents a current, rigorous protocol to evaluate PAI's capability for depth and margin delineation
von Knorring T, 2025	Quantitative chromophore differences (melanin, hemoglobin) between malignant and normal skin	Malignant lesions had significantly higher deoxyhemoglobin (p=0.001). Depth of vascular signals correlated with Breslow depth (r=0.76)	Provides functional (angiographic) and depth data that could guide excision margins based on tumor-associated vasculature	Distinguishing melanoma from benign nevi based on chromophores alone remains challenging	High-quality, quantitative in vivo PAI study directly linking imaging biomarkers to histopathologic depth and diagnosis

Abbreviations: Sens: Sensitivity; Spec: Specificity; NPV: Negative Predictive Value; AUC: Area Under the Curve; HR: Hazard Ratio; CI: Confidence Interval; PNI: Perineural Invasion; DG-HFUS: Dermoscopy-Guided High-Frequency Ultrasound; GTV: Gross Tumor Volume

Table 3

Risk of Bias Summary

Study (First Author, Year)	Assessment Tool	Overall Risk of Bias
Sheng M, 2021	QUADAS-2	Low
Ulrich M, 2016	QUADAS-2	Low
Markowitz O, 2015	QUADAS-2	Low
Ying Y, 2024	QUADAS-2	Low
von Knorring T, 2025	QUADAS-2	Low
Li X, 2025	QUADAS-2	Moderate
Qi X, 2024	QUADAS-2	Moderate
Wang K, 2017	QUADAS-2	Moderate
Sellyn GE, 2025	QUADAS-2	High
Iftimia N, 2016	QUADAS-2	High

Young JJ, 2025	QUADAS-2	High
Papai E, 2025	ROBINS-I	High
Boostani M, 2025	QUADAS-2	High
Karia PS, 2017	ROBIS	Low
Hobayan CGP, 2024	ROBIS	High

Authors' Contribution

All authors contributed equally to the development of this article.

Data availability

All datasets relevant to this study's findings are fully available within the article.

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