Performance of Ultrasound for Identifying Morphological Characteristics and Thickness of Cutaneous Basal Cell Carcinoma: A Systematic Review

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Keywords

Ultrasound · Basal cell carcinoma · High-frequency ultrasound · Imaging · Non-melanoma skin cancer

Abstract

Advances in ultrasound technology and non-surgical treatments of basal cell carcinomas (BCCs) have raised the need to study the performance of high-frequency ultrasound (HFUS) in BCCs. We aimed to assess the performance of HFUS in the evaluation of BCCs to formulate recommendations for its uses and conducted a systematic review of the literature to do so. A search of Central, Medline, Embase, CINHAL, and Web of Science was performed using key/MESH terms “ultrasonography” and “basal cell carcinoma” (January 2005–December 2020). We included primary studies reporting biopsy-confirmed BCCs for which the target intervention was ultrasound assessment at 15 MHz or higher frequency. Thirty articles were included, studying a total of 1,203 biopsy-confirmed BCCs. HFUS provides accurate depth measurements, especially for BCCs >1 mm. The definition of lateral margins in vivo needs further studies; however, ex vivo margin assessment seems convincing. There is a diagnostic role for HFUS in identifying higher recurrence risk BCC subtypes,

which can help in risk stratification. Performance of HFUS is significant in BCC management. Pre-surgical scans may support case selection for Mohs. HFUS can improve safety when used to plan brachytherapy treatments, help with case selection and adjunct treatment choice pre-photodynamic therapy. Finally, HFUS can help follow lesions after intervention, particularly non-surgical management, and support the decision to observe or re-intervene. HFUS can enhance clinical practice by providing useful information that cannot be deduced from the clinical examination. It would be recommended to evaluate the extent, mainly depth, and detect the aggressiveness of the BCCs.

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Introduction

Basal cell carcinomas (BCCs) are the most common type of cancer in the Caucasian population, with the lifetime risk of developing a BCC estimated to be equal to or greater than 20% in the United States [1] and an incidence rate that continues to rise in North America, Asia [2], Europe [3, 4], and Australia [5, 6]. Most BCCs occur on the head and neck [7] and while they rarely metastasize (<0.1%)

[8], they can be locally invasive and cause great morbidity [7]. Biopsy remains the gold standard for diagnosis [9]; however, with the development and increasing use of topical, intralesional, photodynamic, laser, and radiation treatments as well as most recently hedgehog inhibitors [10, 11], a non-invasive diagnostic approach can be favored. Imaging techniques such as reflectance confocal microscopy [12], optical coherence tomography [13], and ultrasound have been studied to assess BCCs. Ultrasound's accessibility, non-invasive nature, safety, and ability to provide information in real-time makes it an invaluable tool in the assessment of dermatological lesions, including BCCs. High-frequency ultrasound (HFUS; e.g., ≥ 15 MHz) has high definition and penetration that generates well-demarcated images, and for this reason, it is considered a first-line imaging technique for the assessment of non-melanoma skin cancers [14, 15]. Basal cell carcinomas appear on ultrasound as a hypoechoic dermal or subdermal structure of variable shape that often contains tumoral hyperechoic spots. The number of these spots within one lesion has been used to discriminate high-risk versus low-risk recurrence of BCC subtypes. Doppler assessment of BCCs usually shows low to moderate vascularity [16].

Significant technological advances in recent years in HFUS quality have allowed its applications to expand. Its role goes far beyond diagnostics, as it can help in the lesion characterization and ultimately contribute to surgical planning and monitoring of treatment response. Our systematic review aims to evaluate the performance of HFUS in diagnostic and non-diagnostic capacities for the assessment of BCCs to formulate recommendations for the applications of sonography for BCCs.

Materials and Methods

Search Strategy

A systematic search of Central, Medline, Embase, CINAHL, and Web of Science was performed using key/MESH terms "ultrasonography" and "basal cell carcinoma". References between January 2005 and December 2020 were considered. Primary studies in either English, French, or Spanish with a minimum of 7 histopathologically confirmed BCCs using ultrasound to assess these lesions were included. The initial search yielded 438 references, of which 90 duplicates were removed. The remaining studies were screened by title and abstract for relevance, and 141 articles were assessed in full by three independent evaluators. In total, 30 articles were included (see Fig. 1: PRISMA flow diagram).

Inclusion and Exclusion Criteria

We included primary studies reporting biopsy-confirmed BCCs for which the target intervention was ultrasound assessment at 15 MHz or higher frequency. Studies reporting data on seven or

Fig. 1. PRISMA flow diagram of the systematic review of literature conducted.

more BCCs were considered. Murine studies and conference abstracts were excluded. Studies discussing other NMSC along with BCCs were considered.

Quality Assessment

We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist to evaluate the studies' quality [17]. This tool was created to be used in systematic reviews of diagnostic accuracy studies. Articles received a quality score based on the 14-item checklist (eTable 1; see online suppl. material at www.karger.com/doi/10.1159/000520751). The Oxford Centre for Evidence-Based Medicine levels of evidence were established for each study and grade of recommendations were subsequently derived from these levels. This process was done by two independent authors (A.L.-S., A.S.) [18].

Data Extraction

Three independent authors (A.L.-S., A.S., D.N. – one dermatology resident and two medical students) extracted the data from the 30 studies included. Demographic, lesion characteristics, and general information pertaining to methodology were collected. Each study was categorized according to the uses they made of HFUS: (i) general lesion characteristics (size, depth, margins, invasion), (ii) diagnostic (primary diagnosis of BCC, subtype identification, subclinical and/or contiguous lesion identification), or (iii) management (surgical planning, non-surgical planning, monitoring). Studies may have been attributed more than one main objective.

Table 1. General characteristics of studies included in this systematic review

Study, country	Design	QUADAS score	HFUS maximum frequency**	Population	BCC characteristics	Primary, post-treatment or recurrence	Location of lesions
Alfageme 2019, Spain	Prospective case series	9	18 MHz In vivo	31 patients 17M, 14F Mean age 73.51	31 BCCs: 22 non-infiltrative 9 infiltrative	NR	Face
Ballester-Sanchez 2014, Spain	Cross-sectional study	12	18 MHz In vivo	20 patients 10M, 10F Mean age 67 (51–89)	20 BCCs: 10 superficial 10 nodular	Primary	Face, trunk
Bens 2015, France	Retrospective case series	10	20 MHz In vivo	66 patients Mean age 73 (48–89)	33 BCCs: 8 infiltrative 25 nodular	Primary	Face
Bobadilla 2008, Chile	Cross-sectional study	13	15 MHz In vivo	25 patients 15M, 10F Mean age 69.5 (48–91)	29 BCCs: 27 nodular 1 morpheiform 1 adenoid	Primary	Face
Crisan 2013, Romania	Prospective case series	11	20 MHz In vivo	46 patients 20M, mean age 51.5 26F, mean age 42.3	18 nodular BCCs	Primary	Face, trunk, limbs
Desai 2007, USA	Prospective case series	8	20 MHz In vivo	NR	50 BCCs: 18 superficial 30 nodular 1 morpheiform 1 infiltrative	Primary	NR
Goyal 2017, USA – A*	Retrospective case series	10	18 MHz In vivo	18 patients 9M, 9F Mean age 70 (54–85)	17 BCCs	Primary	Face, ear, scalp, eyebrow, limbs
Goyal 2017, USA – B*	Retrospective case series	10	18 MHz In vivo	14 patients 6M, 8F Mean age 71	9 BCCs: 4 nodular 3 superficial 1 superficial-nodular 1 unspecified	Post eBT treatment (3 recurrences)	NR
Hernández-Ibáñez 2014, Spain	Prospective case series	11	20 MHz In vivo	8 patients 4M, 4F Mean age 66.12 (41–82)	7 BCCs: 5 infiltrative 2 superficial	Recurrences	Scalp, face, chest, back, shoulder, forearm
Hernández-Ibáñez 2017, Spain	Retrospective case series	12	20 MHz In vivo	Nb of patients NR 59%M, 41%F Mean age 68	156 BCCs: 45 superficial 43 nodular 48 infiltrative 7 mixed superficial + nodular 5 superficial + infiltrative 6 nodular + infiltrative 2 non-specific	Primary	Head, neck, trunk, arms

Table 1 (continued)

Study, country	Design	QUADAS score	HFUS maximum frequency**	Population	BCC characteristics	Primary, post-treatment or recurrence	Location of lesions
Hinz 2012, Germany	Prospective case series	12	20 MHz In vivo	10 patients 9M, 1F Mean age 73.8 (62–80)	10 BCCs: 6 superficial 3 solid 1 fibroepithelioma of Pinkus	Primary	Trunk, head, limbs
Jambusaria-Pahlajani 2009, USA*	Cross-sectional study	12	40 MHz In vivo	98 patients 72M, 26F Mean age 63 (18–95)	77 BCCs	Primary and recurrent	Head, neck
Jovanovic 2005, Serbia*	Prospective case series	11	20 MHz In vivo	NR	12 BCCs	NR	NR
Khlebnikova 2018, Russia	Prospective case control	12	75 MHz In vivo	47 patients, 16M, 31F Mean age 64.8 (56–73)	60 BCCs: 35 superficial 22 nodular 3 morpheiform	Primary	NR
Khlebnikova 2020, Russia	Prospective case series	14	75 MHz In vivo	19 patients 10M, 9F Mean age 65.3 (48–82)	27 BCCs	Primary	NR
Lippert 2013, Czech Republic	Prospective case series	10	25 MHz In vivo	56 patients 32M, 24F Mean age 61.9	56 nodular BCCs	NR	Head, face, neck, other
Marmur 2010, USA	Prospective case series	12	20 MHz In vivo	20 patients	9 BCCs: 2 nodular 6 superficial 1 atypical	NR	Head and neck, face, limbs, trunk
Mogensen 2009, Denmark*	Prospective case series	12	20 MHz In vivo	93 patients 44M, 49F Mean age 70.6 (37–90)	23 BCCs	Primary	Face, other
Nassiri-Kashani 2013, Iran	Prospective case series	13	50 MHz In vivo	36 patients 29M, 7F Mean age 63.85 (42–79)	56 BCCs	Primary	Face, other
Pasquali 2016, Spain*	Prospective case series	12	22 MHz In vivo and ex vivo	89 patients 52M, 37F Mean age 74.37	79 BCCs: 56 nodular 15 superficial 8 mixed	Primary	NR
Raszewska-Famielec 2020, Poland	Prospective case series	11	20 MHz In vivo	70 patients 27M, 43F Mean age 69.04 (33–88)	70 BCCs: 40 nodular 18 superficial 3 micronodular 3 morpheiform 6 mixed	NR	NR
Smucler 2012, Czech Republic	Prospective case series	10	20 MHz In vivo	67 patients 38M, 29F Mean age 68.7 (28–85)	75 BCCs: various subtypes including superficial, nodular, and invasive	NR	Face, head and neck, trunk, limbs
Song 2014, South Korea*	Prospective case series	12	17 MHz In vivo	40 patients 15M, 25F Mean age 78.3 (53–92)	10 BCCs: most superficial and nodular 1 morpheiform	NR	Face

Table 1 (continued)

Study, country	Design	QUADAS score	HFUS maximum frequency**	Population	BCC characteristics	Primary, post-treatment or recurrence	Location of lesions
Tormo 2014, Spain	Retrospective case series	10	19 MHz In vivo	33 patients 18M, 15F Median age 78 (43–97)	45 BCCs	Primary	Face, head and neck, trunk, limbs
Uhara 2007, Japan	Retrospective case control	10	30 MHz In vivo	NR	29 BCCs: 26 nodular and/or ulcerated 3 superficial	NR	NR
Vilas-Sueiro 2018, Spain	Prospective case series	12	18 MHz Ex vivo	65 patients 43M, 22F Mean age 76.36	58 BCCs	NR	Face, scalp, trunk, limbs
Wang 2019, China	Retrospective case series	10	50 MHz In vivo	42 patients 18M, 24F Mean age 61.4 (31–86)	46 BCCs: 37 nodular 3 superficial 2 micronodular 1 infiltrative 2 mixed 1 basosquamous	NR	Face, scalp, lower extremity, trunk
Wenande 2020, Denmark	Prospective case series	12	18 MHz In vivo	19 patients M:F ratio 3:1 Mean age 73 (56–89)	19 BCCs: 13 nodular 6 superficial	Primary	Face, scalp, trunk, extremities
Wortsman 2010, Chile*	Retrospective case control	9	15 MHz In vivo	4,338 patients	41 BCCs: 37 nodular 4 morpheiform	Primary and recurrences	NR
Wortsman 2015, Chile	Retrospective case control	11	18 MHz In vivo	31 patients 15M, 16F Mean age 67 (35–92)	31 BCCs: 16 macronodular 8 nodular 5 morpheiform 1 adenoid cystic 1 sclerosing	Primary	Face, scalp, leg

M, male; F, female; NR, not reported; BCC, basal cell carcinoma. * Study reporting pooled data only of BCCs, along with other lesion types. ** Maximum frequency used in the study; however, some of the devices worked with variable frequency probes that allowed accesses to lower frequencies.

Results

Thirty articles were included in our systematic review (Table 1), studying a total of 1,203 biopsy-confirmed BCCs predominantly located on the head and neck. Nineteen studies reported the histologic variant of the lesions, with a total of 785 classified lesions. Of those, 452 (56.7%) were nodular, 171 (21.8%) superficial, 85 (10.8%) infiltrative, 36 (4.6%) mixed, 17 (2.2%) morpheiform, and 32 (4.1%) classified as others. Eighteen investigations included BCCs exclusively [19–36], 4 studied BCCs along with other lesion types but reported data separately for BCCs

[37–40], and 8 other studies reported pooled data of BCCs and other lesion types (eTable 2) [41–48]. Quality assessment revealed QUADAS scores ranging from 8 to 14. Twelve of the 30 studies commented on operator training, of which 5 were radiologists, 4 were dermatologists, 1 was identified broadly as working in medical imaging, 1 was a physician without further specification, and the last one was a HFUS-trained medical school graduate. Only 7 of these studies quantified the operator's experience, ranging from 10 h of training to 15 years of experience.

Table 2. Use of high-frequency ultrasound (HFUS) in determination of morphological characteristics of basal cell carcinomas (BCCs)

	Size				Depth					Margins	Invasion
	US vs. path	US vs. clinical	Subtype differences	Other	US vs. path	US vs. path vs. OCT	US vs. clinical	Subtype differences	Other		
Alfageme 2019			X							X	
Ballester-Sanchez 2014					X						
Bobadilla 2008				X	X					X	X
Crisan 2013					X						
Desai 2007		X					X			X	
Goyal 2017 – A		X					X				
Hernandez-Ibanez 2017				X					X		
Hinz 2012						X					
Jambusaria-Pahlajani 2009										X	
Jovanovic 2005					X					X	
Khlebnikova 2018								X			
Khlebnikova 2020					X						
Lippert 2013									X		
Marmur 2010		X								X	
Mogensen 2009						X					
Nassiri-Kashani 2013	X				X						
Pasquali 2016	X									X	
Smucler 2012							X				
Song 2014				X	X						X
Tormo 2014									X		
Vilas-Sueiro 2018										X	
Wang 2019								X		X	
Wortsman 2010				X					X		X

US, ultrasound; path, pathology; OCT, optical coherence tomography.

Morphological Characteristics: Surface Measurements, Depth, Margins, and Invasion

Twenty-three of the 30 articles included objectified surface measurements, thickness, margin delineation, and/or assessment of local invasion by HFUS, as detailed in Table 2.

Surface Measurements

Ten studies used HFUS to assess the size of BCCs (Table 3). Two studies compared lesion size on HFUS to measurements on histopathology [29, 46]. Both of these showed larger measurements on HFUS. Three studies compared HFUS measurements of BCCs to clinical measurements [22, 39, 41]. One had larger HFUS measurements [22], one had comparable HFUS and clinical measurements [39], and one had smaller HFUS measurements [41]. Alfageme et al. used HFUS to identify sonographic features distinguishing invasive from non-invasive subtypes but did not identify a significant difference in size between these groups [19]. Hernandez-Ibanez et al. used US to assess BCC surface area to categorize the lesions as small or large (< or ≥40 mm²) for subsequent analyses [24]. Three other studies measured lesion dimensions on HFUS without further analysis [21, 47, 48].

Depth

Eighteen studies examined BCC depth using ultrasonography (Table 4). Seven groups exclusively compared HFUS depth measurements to histopathology. Of these, 1 reported negative results [20] while the other six found that ultrasound could offer an accurate representation of BCC thickness [21, 27, 29, 38, 44, 47]. Comparing HFUS vs. histopathology depth, five of the seven studies reported cases with HFUS slightly inferior thickness [20, 21, 29, 38, 47], and the two others reported lesions with larger HFUS depth [27, 44]. Two studies investigated BCC thickness comparisons between HFUS, optical coherence tomography, and histopathology measurements [25, 45]. Both were found to overestimate thickness on HFUS in comparison to histopathology. Three studies compared US depth measurements to clinical estimates of tumor thickness [22, 31, 41]. Two of the total 18 studies measuring depth assessed BCC thickness to understand subtype differences better [26, 34]. One study measured depth with HFUS to determine treatment parameters of high dose-rate brachytherapy [32]. Two studies measured lesion thickness to select BCCs appropriate for laser ablation pre-treatment followed by photodynamic therapy (PDT) [28, 31]. Two other studies recorded depth measurements with HFUS but did not elaborate [24, 48].

Table 3. Use of high-frequency ultrasound (HFUS) in size measurement determination of basal cell carcinomas (BCCs)

	Study	Gold standard	Results
US vs. path	Nassiri-Kashani 2013	Full excision	Width statistically larger on US than on histopathology, low correlation reported for diameter ($r = 0.27$). Largest diameter mean: US $5,996.77 \pm 2,271.783 \mu\text{m}$, pathology $3,891.07 \pm 1,995.452 \mu\text{m}$
	Pasquali 2016**	Full excision	100 skin lesions (79 BCCs, pooled data) Ex vivo vs. histology tumor area: moderate correlation ($r^2 = 0.4940$) Ex vivo vs. in vivo tumor area: moderate correlation ($r^2 = 0.5524$) All measurements obtained histologically tend to be smaller than on HFUS
US vs. clinical	Desai 2007	Clinical	Good correlation of width, depth, and length between clinical and US measurements ($p < 0.0005$) – Length correlation $r = 0.71$ – Width correlation $r = 0.79$ Overestimation of length and width by US in 46/50 cases
	Goyal 2017 – A	US	A statistically significant difference between clinical and US measurements (20 NMSCs, 17 BCCs pooled data) was observed for the second largest diameter ($p = 0.03$), but not for the largest diameter ($p = 0.24$) – Largest diameter mean: clinical 7.55 mm, US 5.79 mm ($p = 0.24$) – Second largest diameter mean: clinical 6.3 mm, US 4.02 mm ($p = 0.03$) – Depth mean: clinical 0.95 mm, US 1.76 mm ($p = 0.02$)
	Marmur 2010	Clinical	No statistically significant difference for length or width. US identified smaller diameters for BCCs but larger for SCCs than clinically Width mean: clinical 0.81 mm, US 0.62 mm ($t = -1.324$, $p = 0.20$) Length mean: clinical 0.85 mm, US 0.70 mm ($t = -1.093$, $p = 0.29$)
Subtype differences	Alfageme 2019	–	Size of infiltrative vs. non-infiltrative BCCs were compared, no significant difference between groups Max BCC diameter for infiltrative 7.65 ± 2.1 mm vs. non-infiltrative 7.25 ± 2.3 mm ($p = 0.34$)
Other	Hernandez-Ibanez 2017	–	US measured surface area to classify lesions as small or large ($<$ or $\geq 40 \text{ mm}^2$) Mean measurements of $8.2 \pm 4.5 \text{ mm} \times 6.1 \pm 3 \text{ mm}$ Mean surface area of $60.42 \pm 71.02 \text{ mm}^2$; median 40 mm^2
	Wortsman 2010	–	Lesion measurements obtained but not reported
	Bobadilla 2008	–	Lesion measurements obtained but not reported
	Song 2014	–	Lesion measurements obtained but not reported
US, ultrasound; path, pathology; OCT, optical coherence tomography; BCC, basal cell carcinoma. ** Includes ex vivo assessment.			

Lateral Margins

Nine studies investigated the margins of BCCs with ultrasound (Table 5) [19, 21, 22, 33, 34, 39, 43, 44, 46]. Six of these articles explored BCC margins in the context of surgical treatment [22, 33, 39, 43, 44, 46], of which two did so in ex vivo specimens [33, 46]. Two authors briefly commented on margins as a reflection of tumor shape [21, 44]. Lastly, two studies attempted to use BCC margin characteristics to distinguish subtypes [19, 34].

Invasion of Adjacent Structures

Three of the 30 studies included used HFUS to assess for adjacent structure invasion (Table 6) [21, 47, 48], specifically ruling out the invasion of cartilage.

Detection and Characterization

Eleven studies explored the diagnostic role of HFUS in detecting BCCs, their specific subtypes, or subclinical lesions, as outlined in Table 7. These studies were not intended to perform a primary diagnosis of BCC because the lesions were first evaluated clinically, then sent to the

Table 4. Use of high-frequency ultrasound (HFUS) in depth measurement determination of basal cell carcinomas (BCCs)

	Study	Gold standard	Results
US vs. path	Ballester-Sanchez 2014	Punch biopsy	No significant association between US and histology. Nodular cases present larger depth differences than superficial BCCs – HFUS found to be less accurate when lesions are very superficial Mean superficial BCC US thickness: 0.32 mm (range 0.1–1.3) Mean superficial BCC Breslow depth: 0.77 mm (range 0.3–1.9) Mean nodular BCC US thickness: 1.71 mm (range 0.1–3.7) Mean nodular BCC Breslow thickness: 2.09 mm (range 1.1–3.1)
	Bobadilla 2008	Full excision	Excellent correlation (ICC = 0.9) between US and histology in 27/29 cases Mean US thickness: 3.7±1.1 mm (range 1.1–5.0) Mean histology thickness: 3.9±1.0 mm (range 1.1–5.2)
	Crisan 2013	Full excision	A strong correlation (98.4%) between US thickness and histological thickness for nodular BCCs Mean US depth: 1.27±0.6 mm Mean histology depth: 1.43±0.7 mm
	Jovanovic 2005	Full excision	Correlation between depth by US and depth by histopathology after excision was very high ($r = 0.98$) In comparison to thickness on histology, tumor thickness obtained by US ($n = 35$, 12 BCCs pooled data): – overestimated in 29/35 cases (absolute value: 0.01 to 0.9 mm and relative value: 0.4% to 62%) – equal in 3/35 cases – underestimated in 3/35 cases (absolute value: 0.11 to 0.51 mm and relative value: 8% to 42%)
	Khlebnikova 2020	Excision or punch biopsy	27 BCCs scanned at both 30 MHz and 75 MHz. Lesions subsequently excised or punch biopsied and divided into thin (<1 mm) and thick (>1 mm) groups according to depth on histopathology Thin group: – no statistical difference between US and histology depth for both 75 MHz ($p = 0.78$) and 30 MHz ($p = 0.339$) – high correlation for 75 MHz ($r = 0.870$) and weak correlation for 30 MHz ($r = 0.339$) Thick group: – no statistical difference observed between US 30 MHz and histology depth ($p = 0.882$) with a very high correlation ($r = 0.951$) – US evaluation at 75 MHz uninterpretable for many cases (lateral and lower boundaries not identified)
	Nassiri-Kashani 2013	Full excision	No statistical difference in tumor depth between US and histology with a moderate correlation ($r = 0.45$) Mean US depth: 1,353.68±656.45 µm Mean histopathology depth: 1,560.71±1,044.32 µm
	Song 2014	Full excision	Excellent correlation (ICC 0.953) for US and histology of all lesions, very good correlation (ICC 0.89) for the 10 BCCs exclusively as calculated per Table 3 measurements available Mean US depth: 3.97±3.15 mm (range 0.80–14.00) Mean histological depth: 4.04±2.92 mm (range 1.00–14.00)
US vs. path vs. OCT	Hinz 2012	Full excision	Moderate correlation (ICC 0.59) for US and histology; higher correlation (ICC 0.83) for OCT and histology – Both HFUS and OCT measurements were statistically similar to measurements on histopathology, per our analyses of paired T-tests comparing measurements available in Table 1 Mean US depth: 1.03±0.51 mm (range 0.30–2.10) Mean histopathology depth: 0.82±0.46 mm (range 0.15–1.50) Overestimation of depth on HFUS (in comparison to histopath); underestimation of depth on OCT (in comparison to histopath)
	Mogensen 2009	Punch biopsy	Overestimation of depth was found with US with a significant difference observed between US and histology ($n = 34$, 23 BCCs pooled data) Mean US depth: 1,552±722 µm Mean histopathology depth: 821±470 µm

Table 4 (continued)

	Study	Gold standard	Results
US versus clinical	Desai 2007	Full excision	Clinical and US measurements correlated well in terms of depth ($p > 0.0005$) Lesion measurements obtained but not reported
	Goyal 2017 – A	Punch biopsy	Depth obtained with US was significantly different from clinical estimates ($p = 0.02$). Clinical measurements were found to underestimate the depth of the lesion compared to US (20 NMSCs, 17 BCCs pooled data) Mean US depth: 1.76 ± 1.28 mm Mean clinical depth: 0.95 ± 1.10 mm
	Smucler 2012	US	75 BCCs were divided according to tumor depth on HFUS into one of three groups: A) <2 mm, B) $2-3$ mm, and C) >3 mm. Each group had specific treatment protocols ** US measurements are considered as the gold standard and are compared to clinical depth estimated by an experienced dermatologist** Clinical assessment of depth was incorrect compared to US in 10/75 lesions Lesion measurements obtained but not reported
Subtype differences	Khlebnikova 2018	–	Statistically significant increase in mean depth of nodular and morpheiform variants compared to superficial BCCs ($p < 0.05$) Mean US depth superficial BCC: 556.28 ± 136.95 μ m Mean US depth nodular BCC: $2,439.71 \pm 865.92$ μ m Mean US depth morpheiform BCC: $1,500 \pm 325.33$ μ m
	Wang 2019	–	Low-risk and high-risk lesions exhibited a significant difference in depth. Lesion measurements obtained but not reported
Other	Tormo 2014	–	Median US depth: 2 mm (range 0–4)
	Lippert 2013	–	Lesion measurements obtained but not reported
	Hernandez-Ibanez 2017 –	–	Lesion measurements obtained but not reported
	Wortsman 2010	–	Lesion measurements obtained but not reported

US, ultrasound; path, pathology; OCT, optical coherence tomography; BCC, basal cell carcinoma; AK, actinic keratosis.

ultrasound examination, and finally confirmed on pathology.

Two studies evaluated the performance of HFUS to detect the location and characteristics of the primary tumors [40, 48]. Three investigations either sought to identify specific BCC subtypes with the help of HFUS [26, 37] or described sonographic characteristics of subtypes [22]. Five studies aimed to find sonographic differences between low-risk and high-risk subtypes of BCCs [19, 23, 24, 34, 36]. Subclinical discrete or contiguous BCCs were identified on HFUS in three different studies [21, 34, 48].

Hyperechoic spots were very informative to stratify BCCs by severity and to identify certain specific subtypes. More than 3 hyperechoic spots located both centrally and in the periphery were identified to be characteristic of nodular BCCs, and more than seven hyperechoic spots were used as a cut-off for identifying high-risk of recurrence BCCs [26, 37]. Further, marginal stiffness was found to be a feature of infiltrative BCCs [19]. Other studies identified irregular shape and subcutaneous tissue in-

volvement as characteristic of high-risk BCCs [34]. Five different studies explored the diagnostic value of hyperechoic spots [19, 26, 34, 36, 40], but only one described a systematic approach to counting them [36].

Management

Eleven of the 30 studies, detailed in Table 8, used HFUS to manage BCCs, either for planning surgical or non-surgical treatment or monitoring response to treatment. Ultrasound modified surgical planning in three studies by identifying satellite lesions, by ruling out the presence of cartilage invasion [21, 47], or by using HFUS to outline depth, height, and width [22, 47], which subsequently guided reconstructive options. Desai et al.'s excision with 4-mm margins on HFUS-delineated BCCs resulted in a 10% margin positivity rate [22], which is in line with prior studies showing tumor clearance rates of 92% with clinically outlined BCCs [49]. It is argued that HFUS may not have been used to its full potential in this study as the 5 lesions with positive margins presented sonographic

Table 5. Use of high-frequency ultrasound (HFUS) in margin assessment of basal cell carcinomas (BCCs)

	Study	Used for excision	Results
In context of surgical treatment	Desai 2007	US	Margin assessment consistently showed a mean 20% to 25% increase compared to clinical measurements ($p < 0.0005$)
	Jambusaria-Pahlajani 2009	Clinical	Tumor map generated outlining peripheral margins of lesions on US assessment pre-Mohs (test) and overlaid with the histopathology tumor map post first stage of Mohs (gold standard) ($n = 98$, 77 BCCs pooled data) <ul style="list-style-type: none"> – Sensitivity 32%, specificity 88%, PPV 47%, and NPV 79%, correct classification 73% for US delimitation of margins compared to tumor map from histopathology – Sensitivity 80% (95% CI 28–99) and specificity 84% (95% CI 69–94) for larger tumors (area $> 1.74 \text{ cm}^2$) with histologically positive margins only in the dermis
	Marmur 2010	Clinical	Margins delineated clinically (used for Mohs) and assessed by US in 9 BCCs <ul style="list-style-type: none"> – 4 BCCs required multiple stages: all had smaller size on US than clinically – 2 BCCs required 1 stage of Mohs but assessed as larger on US than clinically – 3 BCCs required 1 stage of Mohs but assessed as smaller on US than clinically
	Jovanovic 2005 [†]	US	Tumor margins on US correlated very well with histopathology
	Pasquali 2016**	US	Margins assessed pre and post excision on HFUS and compared to histology (84 NMSC, 79 BCCs pooled data): <ul style="list-style-type: none"> – 81 had a correspondence between ex vivo HFUS and histology margins (77 negative SM, 4 positive SM on both ex vivo HFUS and histology) – 2 had negative SM by ex vivo HFUS while positive SM by histology (i.e., incorrect US) – 1 indeterminate scan
	Vilas-Sueiro 2019**	Clinical	Excisions with 2–3 mm margins assessed clinically. Ex vivo specimen examined by HFUS prior to histopathology showed: <ul style="list-style-type: none"> – Lateral margins: mean 1.61 mm (range 0–3.8 mm) – Deep margins: 2.05 mm (range 0–5.7 mm) Ability to predict margin involvement: specificity 91.66% and NPV 96%
Tumor shape	Bobadilla 2008	–	Tumor-free borders on histology in 100% of cases after full excision guided by US
	Jovanovic 2005 [†]	–	Tumor shape on US correlated very well with histopathology
Subtype differences	Wang 2019	–	High risk and low risk BCC US margins did not differ significantly ($\chi^2 = 3.231$, $p = 0.072$)
	Alfageme 2019	–	Increased marginal stiffness was statistically greater in infiltrative BCCs (88%) than non-infiltrative (19%). Study characteristics for marginal stiffness of: <ul style="list-style-type: none"> – infiltrative BCC: sensitivity 89%, specificity 82%, PPV 67% – non-infiltrative BCCs: NPV 95%

US, ultrasound; HFUS; high-frequency ultrasound; PPV, positive predictive value; NPV, negative predictive value; BCC, basal cell carcinoma; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; SM, surgical margin. ** Includes ex vivo assessment. [†]Study appearing twice in table.

findings that could have prompted a referral to Mohs (unclear boundaries and asymmetric growth patterns) instead of going forward with the excision [22].

Four studies used ultrasound to either select the best treatment for BCCs or to choose optimal parameters of a given non-surgical treatment. Two of these did so with brachytherapy [32, 41]. Ultrasound proved to be accurate to assess tumor dimensions and to inform the prescription parameters for brachytherapy [32, 41]. Excellent clearance rates were reported, compatible with previous studies showing local control rates of 98.7% for

eBT-treated NMSC [50]. The main advantage of US was to minimize toxicity by having an objective measurement keeping the prescription depth at a strict minimum. Toxicity for both studies was $\leq$ grade 1 in 100% of patients [32, 41], while a prior eBT study assessing 154 NMSC of which 149 were BCCs reported only 52.6% grade 0–1 acute radiation dermatitis and 94.62% grade 0–1 late toxicity [50]. Two studies treated BCCs with PDT regimens and used HFUS to optimally select parameters or adjunct treatments [28, 31]. Both studies included in our review aimed to identify optimal treat-

Table 6. Use of high-frequency ultrasound (HFUS) in assessment of invasion of adjacent structures by basal cell carcinomas (BCCs)

Study	Adjacent structures examined	Results
Bobadilla 2008	Cartilage	16 out of 29 BCCs assessed for invasion of the nasal cartilage – None showed signs of tumor involvement in the cartilage on HFUS – Influenced the decision to not remove any cartilage, pathology later confirmed margins were tumor free
Song 2014	Cartilage	47 skin lesions (10 BCCs) involving the head and neck were assessed for local invasion – None of the lesions invaded cartilage
Wortsman 2010	NR	41 BCCs, distance between lesions and surrounding structures was recorded – No specific mention of invasion or absence thereof is made when reporting the findings
NR, not reported.		

Table 7. High-frequency ultrasound (HFUS) diagnostic applications for detection and characterization of basal cell carcinomas (BCCs)

	Study	Results
Detection	Uhara 2007	29 BCCs and 56 melanomas were classified into 4 patterns of HS: A = multiple >5 spots, B = sparse 3–5 spots, C = multiple moderate, D = sparse moderate – BCCs: 14/29 A; 7/29 B; 3/29 C; 5/29 D. All superficial BCCs (3/29) were pattern D – Melanomas: 0/56 A, B, C; 3/56 D – HS correlated with calcifications, cornified cysts, or clusters of apoptotic cells on histopathology
	Wortsman 2010	Clinical diagnosis compared to combined clinical and US diagnosis ($n = 75$ skin and nail malignant lesions of which 41 BCCs, pooled data reported): – There was no significant difference between correct diagnosis of malignant lesions with clinical assessment alone (87%) compared to combined with US (91%) ($p = 0.62$)
Individual subtype identification	Bens 2015	Retrospective examination of US scans of lesions where there was hesitancy in clinical diagnosis between nodular BCC and sebaceous hyperplasia ($n = 77$ of which 33 BCCs) – Echogenicity was qualitatively recorded for each lesion (hypoechoic vs. iso/hyperechoic) → hypoechoic established as diagnostic criteria for BCCs – Sensitivities of 90.9% for nodular BCCs and 81.3% for infiltrative BCCs reported
	Khlebnikova 2018	60 BCCs scanned at 30 MHz and 75 MHz to describe sonographic patterns of superficial, nodular, and morpheiform BCCs – HS were reported in 11% of superficial BCCs and 100% of nodular BCCs – Superficial BCCs had 1–3 dots while nodular BCCs had 1–26 → >3 HS considered characteristic of nodular subtype – Superficial BCCs had HS in the periphery while nodular BCCs had HS in center and periphery – Thickness of the hypoechoic zones was found different between superficial and nodular BCCs and for superficial and morpheiform BCCs but not for nodular and morpheiform BCCs
	Desai 2007	Study included clinically appearing nodular and superficial BCCs – 2 BCCs resulted as morpheiform and infiltrative on histopathology. This was strongly suspected on HFUS as strikingly different patterns were noted and boundaries seemed unclear – Ultrasonographic findings described for morpheiform, infiltrative, superficial, and nodular BCCs

Table 7 (continued)

	Study	Results
Low-risk vs. high-risk classification	Alfageme 2019	Characterization of infiltrative (22/31) vs. non-infiltrative (9/31) BCCs using elastography. Statistically greater strain ratios (marginal stiffness) were recorded at the periphery of infiltrative compared to non-infiltrative BCCs: <ul style="list-style-type: none"> – Sensitivity 89%, specificity 82%, PPV 67%, and NPV 95% for non-infiltrative BCCs – Size, vascularization, or hyperechoic dots were not significantly different between the 2 groups
	Hernandez-Ibanez 2014	Assessment of 8 clinically suspected recurrences in non-surgically treated BCCs. Each suspected recurrence was scanned, then punch biopsied and finally excised. US appearance classified as aggressive vs. non-aggressive lesions, then classification compared to histopathology: <ul style="list-style-type: none"> – US correctly identified 4/5 infiltrative BCCs but 0/2 superficial BCCs – One lesion was non neoplastic but identified as non-aggressive on US
	Hernandez-Ibanez 2017	156 BCCs were scanned, then punch biopsied, and finally excised. US appearance classified as invasive vs. non-invasive, then classification was compared between HFUS and excision histopathology as well as between punch and excision histopathology: <ul style="list-style-type: none"> – Agreement with excision was 73.7% for US and 79.9% for punch biopsy – US sensitivity 74.5% and specificity 73% vs. punch biopsy sensitivity 76% and specificity 82% for detection of invasive lesions – Subtype analysis: Sensitivity with punch biopsy was better for nodular BCCs. US was more specific and better PPV (US 93.3% vs. punch biopsy 92%) for superficial BCCs Subtype identification based on surface area of lesions: <ul style="list-style-type: none"> – Small BCCs (<40 mm²): agreement with excision was 70.4% for US and 86.4% for punch biopsy – Large BCCs (>40 mm²): agreement with excision was 77.3% for US and 72.6% for punch biopsy – As lesions got larger, diagnostic ability of US improved while that of punch biopsy decreased Mixed subtypes lesions: <ul style="list-style-type: none"> – High NPV (>95%) for both US and punch biopsy – Punch biopsy better than US for PPV, sensitivity, and specificity
	Wang 2019	Review of 46 BCC US scans (6 high-risk and 40 low-risk). Multiple parameters were described per specific BCC subtype and subsequently compared to see if any of these parameters would be discriminant between low-risk vs. high-risk lesions <ul style="list-style-type: none"> – US identified high-risk lesions with irregular shapes and infiltration into the subcutaneous tissue – No significant difference observed to classify high-risk vs. low-risk lesions based on HS since 76% of BCCs displayed them
	Wortsman 2015	31 BCCs examined by HFUS to determine predictors of low vs. high recurrence risk subtypes, particularly focusing on hyperechoic spots. A systematic approach to counting these spots was outlined <ul style="list-style-type: none"> – All BCCs were found to have these characteristic spots – Statistical difference was observed for high recurrence risk (mean 8, range 4–81) vs. low recurrence risk (mean 5.5, range 3–25) – A cut-off of 7+ hyperechoic spots for high-risk recurrence prediction offered the best discrimination (sensitivity 79% and specificity 53%)
Subclinical lesions	Bobadilla 2008	2 satellite lesions on nose were identified by US in a patient with 1 clinically visible BCC (<i>n</i> = 29 BCCs)
	Wang 2019	5 subclinical lesions were identified on US out of 46 BCCs: <ul style="list-style-type: none"> – 1 discrete: micro-nodular – 4 contiguous: 3 nodular and 1 mixed nodular and sclerosing
	Wortsman 2010	2 satellite lesions were identified on US out of 41 BCCs
HS, hyperechoic spots; US, ultrasound; HFUS, high-frequency ultrasound; PPV, positive predictive value; NPV, negative predictive value.		

Table 8. High-frequency ultrasound (HFUS) management applications for basal cell carcinomas (BCCs)

	Study	Results
Surgical planning	Bobadilla 2008	27 clinical BCCs examined, one of which had 2 subclinical lesions found by US → change of surgical plan to a frontal flap to excise all 3 lesions <ul style="list-style-type: none"> – Cartilage involvement of the nose ruled out by US – Depth of all the incisions was guided with US evaluation
	Desai 2007	Depth, height, and width of 50 BCCs were outlined by US and excised with 4 mm margins. 5/50 had positive margins <ul style="list-style-type: none"> – 2 nodular, 1 superficial, 1 morpheiform, and 1 infiltrative – All 5 were located on masked area of face (increased scanning difficulty)
	Song 2014	47 skin lesions (10 BCCs, pooled data) scanned by US prior to surgical excisions (3–5 mm margins) <ul style="list-style-type: none"> – Local invasion of cartilage ruled out – Depth and size identified by US were used to choose reconstructive options – Unclear how many of the 10 BCCs had positive margins but mention that 1 morpheiform BCC was not cleared with 4 mm margins
Non-surgical planning – brachytherapy (BT)	Goyal 2017 – A	20 NMSCs (17 BCCs, pooled data) assessed by HFUS <ul style="list-style-type: none"> – Size on US used to choose applicator dimensions for eBT – Thickness on US used too to determine prescription depth – 4 lesions could not be assessed by US and depth was prescribed at 1 mm All patients had a complete response on follow-up clinical assessment; toxicity was at most grade 1
	Tormo 2014	45 BCCs assessed by HFUS to determine depth <ul style="list-style-type: none"> – US used for prescription depth for HDR-BT (<3 mm or between 3 and 4 mm) 98% complete regression at 47 months; toxicity was at most grade 1 Lesions ≥4 mm were excluded as to not exceed acceptable radiation doses
Non-surgical planning – photodynamic therapy (PDT)	Lippert 2013	Aimed to assess the efficacy of ablative fractional photothermolysis (AFP) as an adjunct to PDT for nodular BCCs thicker than 2 mm. US was used to: <ul style="list-style-type: none"> – assess eligibility of BCCs for LA + PDT (<2 mm; control) vs. LA + AFP + PDT (>2 mm; test) – assess laser ablation depth Laser ablation + PDT had clearance rate of 80.4% vs. 92.9% for laser ablation + AFP + PDT at 18 months; toxicity was at most grade 1
	Smucler 2012	US was used to classify depth of 75 BCCs into 3 groups Clearance rates observed at 6 months: Group A (PDT alone, <2 mm, <i>n</i> = 44): 81.2% Group B (PDT + Er:YAG, 2–3 mm, <i>n</i> = 19): 94.7% Group C (PDT + diode laser, >3 mm, <i>n</i> = 12): 100% Toxicity was at most grade 1
Monitoring	Goyal 2017 – B	US was used to: <ul style="list-style-type: none"> – assess lesions pre and post eBT treatment to monitor recurrences at 6 months – distinguish residual disease from post eBT inflammatory changes At follow-up: <ul style="list-style-type: none"> – Clinically, there was no apparent lesion – On US, 11/14 NMSCs (6/9 BCCs) showed no residual disease and 3/14 NMSCs (3/9 BCCs) were reduced in size. Specific measurement improvements are provided for each PR patient. These 3 cases were followed up more closely by the treating radiation oncologist and dermatologist
	Hernandez-Ibanez 2014	US and punch biopsy were compared to excisional biopsy to study recurrences in 8 BCCs post treatment (non-surgical) and to classify aggressivity of lesion <ul style="list-style-type: none"> – US correctly identified 4/5 infiltrative and 0/2 superficial BCCs – Punch biopsy correctly identified: 1/5 infiltrative and 2/2 superficial BCCs
	Wenande 2020	US, OCT, and RCM were compared in monitoring of response to treatment of 19 BCCs with combined AFP and dual topical chemotherapeutic agents Follow-ups at 30 days and 3 months both showed that HFUS was not helpful for differentiating clearance vs. residual disease compared to OCT and RCM

Table 8 (continued)

Study	Results
Raszewska-Famielec 2020	<p>70 BCCs monitored by US post treatment (4, 12, 24 weeks)</p> <p>Nodular BCCs – surgically managed:</p> <ul style="list-style-type: none"> – 6/40 had positive margins <ul style="list-style-type: none"> ○ 4/6 had hypo/heteroechoic foci on US follow-up confirming disease recurrences ○ other 2/6 were disease free at 24 months – 10/40 had narrow (<0.2 cm) margins <ul style="list-style-type: none"> ○ only 1/10 showed residual disease <p>Superficial BCCs – surgical (15/18) and non-surgical (3/18) management:</p> <ul style="list-style-type: none"> – All surgical had negative margins and negative US follow-ups – Of the non-surgically managed (ALA-PDT) lesions <ul style="list-style-type: none"> ○ 2/3 had negative US scans ○ 1 had US findings of recurrence so treated again with imiquimod <p>The remaining 12 BCCs (micronodular, morpheiform, and mixed) were excised and showed no residual disease on US at 24 months</p> <p>* Hypo or heteroechogenic foci seen in nodular BCC follow-ups are suggestive of residual disease or recurrence if they are enlarging from one study to another</p> <p>* HFUS was found to be of particular benefit in monitoring lesions that were managed non-surgically</p>

US, ultrasound; HDR-BT, high dose rate brachytherapy; LA, laser ablation; PDT, photodynamic therapy; AFP, ablative fractional photothermolysis; eBT, electronic brachytherapy; OCT, optical coherence tomography; RCM, reflectance confocal microscopy.

ments for thicker BCCs [28, 31], considering that current evidence suggests that PDT should only be used for lesions with a depth of 2 mm or less due to poor clearance rates with thicker tumors [51–54]. The first study showed that AFP was an effective strategy to improve the penetration of the photosensitizing agent prior to PDT [28]. The second study showed that BCCs with a depth of 2–3 mm and >3 mm could result in clearance rates of 94.7% and 100%, respectively, with different adjunctive laser treatments pre-PDT [31].

Four studies used HFUS to monitor response to treatment and recurrences [23, 30, 35, 42]. These studies included BCCs largely treated non-surgically [23, 35, 42]. Only one study included surgically managed BCCs [30]. Two of these four studies did not find HFUS to be helpful for monitoring [23, 35]. However, it was noted that HFUS was particularly helpful in lesions managed non-surgically to characterize residual disease and recurrences over time [30]. Positive margins significantly increase the risk of recurrence of BCCs, but the literature reports that this risk may vary between 26 and 38.5% (compared to 5.9–14% if margins are negative) [55–57]. Along with risk factors discussed in these studies [55–57], HFUS could have a role in identifying which lesions would be more prone to recur, as Raszewska-Famielec’s group followed 2 BCCs with positive margins post-excision with interval US screening [30]. The absence of disease on sonographic as-

essment informed the decision to monitor rather than re-intervene, and no recurrence was noted during follow-up [30].

Devices, Spatial Resolution, and Operator Training

A variety of machines from 10 different companies were used (1 study did not report equipment details) with different processors, probes, and examination parameters. Axial and lateral spatial resolutions reported in 10 of the 30 studies varied widely, respectively, between 50 and 100 μm and between 21 and 500 μm , which likely had a significant impact on the quality of the images obtained and the conclusions that could be drawn from these assessments. We also noted a high variability in operator training throughout the different studies. Eighteen of the 30 studies did not comment on operator experience, making it more difficult to interpret these results.

Discussion

Our review proved that HFUS can be used as a primary imaging modality to study BCCs. HFUS provides accurate depth measurements, especially for thicker BCCs (>1 mm). When assessing thickness in more superficial lesions, one should consider higher frequencies such as ≥ 70 MHz, although we recognize this is not wide-

Table 9. Recommended uses for high-frequency ultrasound (HFUS) in the assessment of BCCs

Recommendations based on our review	No. of studies by level of evidence	Grade of recommendation
<i>Morphological characteristics</i>		
Surface measurements	2 level 3b studies [21, 48]	C
HFUS did not seem more useful than clinical assessment for the determination of surface measurements; further research is needed, particularly with UHFUS*	8 level 4 studies [19, 22, 24, 29, 39, 41, 46, 47]	
Depth	4 level 3b studies [20, 21, 26, 48]	B
- HFUS provides accurate depth measurements, especially for thicker BCCs (>1 mm)	14 level 4 studies [22, 24, 25, 27–29, 31, 32, 34, 38, 41, 44, 45, 47]	
- When assessing thickness in more superficial lesions, one should consider UHFUS		
Lateral margins	2 level 3b studies [21, 43]	C
- Further research is needed for applicability in vivo considering UHFUS	7 level 4 studies [19, 22, 33, 34, 39, 44, 46]	
- May be a role for ex vivo margin assessment		
Invasion of adjacent structures	2 level 3b studies [21, 48]	B
Can rule out BCC invasion of adjacent cartilage	1 level 4 study [47]	
<i>Diagnosis – detection and characterization</i>		
Detection of primary lesions	2 level 3b studies [40, 48]	B
It can detect and characterize the primary lesions; however, further research is needed with UHFUS		
Individual subtype identification	1 level 3b study [26]	C
It may support the identification of the subtypes; however, further research is needed with UHFUS	2 level 4 studies [22, 37]	
Low-risk vs. high-risk classification	1 level 3b study [36]	B
Can reliably help identify higher recurrence risk BCC subtypes	4 level 4 studies [19, 23, 24, 34]	
Subclinical lesions	2 level 3b studies [21, 48]	B
Can help in identifying subclinical lesions (discrete and contiguous)	1 level 4 study [34]	
<i>Management</i>		
Surgical planning	1 level 3b study [21]	C
Pre-surgical scans can provide information on local invasion and inform case selection for Mohs	2 level 4 studies [22, 47]	
Non-surgical planning (BT and PDT)	4 level 4 studies [28, 31, 32, 41]	C
- Can reliably help determine the minimal prescription depth, thus minimizing treatment-associated toxicity		
- Can help with case selection		
- Can help with adjunct treatment choice pre-PDT		
Monitoring	4 level 4 studies [23, 30, 35, 42]	C
- Can help follow lesions after intervention to assess response to treatment and monitor for recurrences (particularly for non-surgically managed BCCs)		
- Can inform decision to observe vs. re-intervene		
* UHFUS, ultra high-frequency ultrasound (i.e., ≥30 MHz; however, ≥70 MHz, would be better suited for most superficial BCCs).		

ly available. Lateral margin determination in vivo for BCCs did not show convincing evidence for applicability, but there may be a role for ex vivo margin assessment. There appears to be a diagnostic role for HFUS in identifying higher recurrence risk BCC subtypes, which can help in risk stratification. It was consistently observed that HFUS performed better in assessing depth, margins, and identifying aggressive compared to non-aggressive

BCC subtypes for larger tumors. Performance of HFUS is significant in the management of BCCs. We note that pre-surgical scans can provide information on local invasion and inform case selection for Mohs. HFUS can improve safety when used to plan brachytherapy treatments and help with case selection and adjunct treatment choice pre-PDT. Finally, HFUS can help follow lesions after intervention, particularly non-surgical management, over

time and possibly inform the decision to observe or re-intervene (Table 9).

A tendency towards overestimation of length and width for HFUS was noted compared to both clinical and histopathology measurements. This was the case in both in vivo and ex vivo specimens [22, 29, 46]. On histology, overestimation is usually due to inflammation surrounding the tumor, and it usually represents a smaller difference in diameter than what the safety margin would be in the context for a given BCC excision [21, 22]. It is also thought that tissue shrinkage occurring during the processing of a sample for histopathology could explain these discrepancies [21].

Overall, HFUS accurately assessed the depth of BCCs. Of the studies exclusively comparing US depth to histopathology, 6/7 studies reported a moderate to strong correlation. The single study that found no significant association between HFUS and histopathology depths used punch biopsy only as a gold standard [20], while others used full excision. The selection of the biopsy area involves a clinical suspicion of the thickest part of the lesion, which is subject to error. Thus, biopsy may not have captured the deepest point of the lesion.

Several studies reported that depth was overestimated on US assessment [25, 27, 44, 45], which is the more widely accepted notion. Contrary to this, 5 investigations reported that HFUS underestimated depth [20, 21, 29, 38, 47]. It has been shown that the excision of a lesion leads to a loss of skin tension, which could result in a greater measured thickness on histopathology. However, this is usually countered by the shrinkage that can occur with fixation, dehydration, and embedding [58]. Crisan et al. proposed that US depth underestimations could be explained by the vascular nature of BCCs that make them more compliant, thus more subject to being mechanically compressed during the US assessment; however, compression during dermatologic examinations is not usually performed because the technique uses a pad of gel on top of the lesion [16, 38]. Performing an US evaluation after a biopsy will naturally cause some alterations to the lesion's anatomy, contributing to some inflammatory and scar changes depending on the time between biopsy and scan. It is also possible that the deepest part of the tumor was removed on biopsy. Most of the studies performed biopsies or excisions after US; otherwise, sonographic assessments were performed at 1 month post biopsy [20], or they purposefully excluded lesions that had received any types of treatment (drug or surgical) 1 month prior [34].

HFUS requires training of the operators like any other imaging technique, limiting the implementation of the

technique in some institutions [59]. The variety of devices and the level of training of the operators may affect the accuracy of the results; however, in this context, ultrasound still seems worthwhile.

In the last few years, technological developments have added ultra-high frequency ultrasound (UHFUS) to the arsenal of dermatological sonography, consisting of assessments at frequencies ranging from 30 MHz up to 100 MHz [60]. The axial spatial resolution of such a technique is approximately 30 μm at 70 MHz [61, 62] and allows for exceptional visualization of superficial structures, therefore ≥ 70 MHz would be better suited in superficial BCCs. In deeper lesions lower frequencies are needed because UHFUS has lower penetration. Nowadays, most new ultrasound technologies (HFUS and UHFUS) use variable frequency probes to manage the detection depth so the operator can move between frequencies and adapt the frequency to the depth of the lesion. UHFUS has opened the door to a variety of applications in different disciplines of medicine, but within the dermatological world, it has been used to explore a myriad of pathologies, including oral mucosa disease [63–65], hair pathology [66], systemic sclerosis [67], adnexal tumors [68, 69] as well as melanocytic lesions [70], the latter having been largely excluded from conventional HFUS applications. To the best of our knowledge, three studies have thus far investigated the use of UHFUS in BCCs [29, 71, 72], of which only Nassiri et al. [29] was included in our review as the other two studies only examined one BCC each.

HFUS evaluations of BCCs are not meant to replace histopathology but can enhance clinical practice by providing valuable management-altering information. The technique is safe (non-radiating) and provides real-time insights into the characteristics of the tumor.

Conclusion

In conclusion, HFUS is an imaging technique that supports the diagnosis and management of BCCs. It would be recommended to assess the extent, mainly depth, and the aggressiveness of the lesions.

Key Message

We recommend using ultrasound to evaluate the depth and aggressiveness of basal cell carcinomas.

Statement of Ethics

Ethical review and institutional approvals were not required as study is based solely on published literature.

Conflict of Interest Statement

Dr. Ximena Wortsman: received royalties for books from Springer and a Speaker Bureau from Abbvie. No other authors have conflicts of interest to declare.

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Author Contributions

A.L.S., A.S., and D.N. performed the literature search and wrote and reviewed the manuscript; A.J., A.A., and E.O. wrote and reviewed the manuscript; X.W. wrote and reviewed the manuscript and supervised the research activities. The authors confirm they have not published, posted, or submitted any related papers from this study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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