Review Article

The Role of High-Frequency Ultra Sound (HFUS) in Skin Malignancy: A Literature Review

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Abstract

High-frequency ultrasound (HFUS) has a significantly reduced tissue penetration depth that provides superior resolution images of tissues and structures near the skin's surface. HFUS is one of the examinations that can be performed to assess skin tumours before and after biopsy or surgery, even after therapy. The utilization of HFUS in skin malignancies covers diagnosis, staging and treatment phases. HFUS provides information about tumour features such as size, shape, depth, consistency, and vascularity, that can be done before an invasive skin biopsy or surgery. HFUS is a supporting examination and a non-invasive tool to plan the treatment of certain skin tumours. In addition, HFUS can assess prognosis in some cases that require additional management. The final diagnosis of skin tumour types is not completely feasible by using the HFUS, because it is unable to distinguish between benign and malignant tumours. Another limitation is that it cannot give tissue diagnostics. HFUS cannot discriminate between tumour and inflammatory infiltrates, which may result in overestimation of tumour dimensions. It is important to emphasise that HFUS should not be utilised as a standalone diagnostic tool, but rather in conjunction with clinical examination and histopathological findings to help reach a definite diagnosis and treatment approach.

Keywords: HFUS, ultrasound, skin malignancy, skin tumor, diagnosis.

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Introduction

Skin malignancy is the most prevalent type of cancer worldwide. According to the American Cancer Society's most recent estimates, 3.3 million persons were diagnosed with nonmelanoma skin cancer in 2012. Keratinocyte cancer is the most prevalent of the different forms of skin cancer. Keratinocyte cancer includes both squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Malignant melanoma's prevalence was about only 2% of all skin cancer occurrences, but it causes 80% of skin cancer deaths. These findings have prompted many campaigns and efforts to emphasize prevention and early detection of skin cancer.[1]

The quicker skin cancer is managed, the lessprobable it is to cause local tissue damage, metastasis, and death. In general, skin cancer screening involves a visual, dermoscopic examination of the lesion, followed by a biopsy and histopathologic evaluation. Biopsy and histopathologic investigations constitute the gold standard in the diagnosis of skin cancer, although they have certain limitations.[2] Skin biopsy requires processing of the biopsy which will then be analyzed by a specialized histologist, thus this process requires a specialized expert who is trained. Access to these diagnostic

approaches may be difficult and beside of emergency cases usually takes times in many health services. This results in delayed or inappropriate treatment for patients.[3] Complications may also arise with skin biopsy procedures, even though it is a safe and easy procedure. Post-operative complications such as wound infection and bleeding may occur.[4] In addition, inadequate depth of tumor biopsy can lead to misdiagnosis. A single biopsy examination cannot detect the complete microscopic characteristics in cases of heterogeneous tumors. Therefore, some tumor masses require multiple biopsies to confirm the diagnosis.[5]

Many innovative skin cancer detection technologies have been studied recently, with the aim of improving the diagnostic accuracy of skin malignancy. The new technologies are less invasive than biopsy, making them a preferable option for lesions in cosmetically sensitive areas or patients with a history of hypertrophic scar formation.[2] An objective, noninvasive examination in addition to the clinical examination in assessing the size, shape, characteristics and depth of skin tumors. This examination is particularly useful if performed prior to biopsy. HFUS is one of the examinations that can be performed to assess skin tumours before and after biopsy or surgery, even after therapy.[5] HFUS was used to diagnose 4338 skin lesions before biopsy in a study conducted by Wortsman and colleagues. This study discovered that clinical examination alone was 73% accurate for lesion diagnosis, but clinical examination plus HFUS was 97% accurate with an overall sensitivity of 99% and specificity of 100%.[2]

This review aims to understand and discuss the role of HFUS in skin malignancies that will be useful in increasing insight into achieving appropriate skin malignancy management as a supporting examination and a non-invasive tool to plan the diagnosis, staging and treatment of skin malignancy. This article was reviewed between February and July 2024.

Review

Ultrasound imaging is a technique for creating images using ultra-high frequency sound. Sound is a vibration of mechanical energy. Ultrasound, as a medical imaging tool, is generated by specific crystalline materials that, when electrically activated, can vibrate at millions of times per second. Transducers are the devices that create and detect ultrasound.[6]

An ultrasound image is produced by the piezoelectric effect, which stimulates mechanical oscillations of the crystal with electrical pulses. Ultrasound waves are reflected by deeper structures when the transducer is placed on the skin. The pulse generator transmits an electrical signal to the transducer, which delivers the ultrasonic pulse to the skin. After that, the propagating ultrasound waves may interact with the tissue, causing reflection, refraction, scattering, absorption, and attenuation. The transducer detects the echoes reflected by the tissues, revealing the acoustic wave-tissue interaction and resulting in ultrasound imaging. The transducer then collects the reflected signal, converts it into an electrical signal, and transmits it to the receiver, which amplifies the entire signal. The signal is altered with time gain compensation to create a scan on the computer, yielding a one-dimensional line graph in amplitude mode (A mode) that can be used to interpret echogenicity at different distances from the probe. Brightness mode (B mode) generates images with varying brightness levels. In this method, the transducer-evaluated tissue is displayed as a real-time image on the device's screen. The acoustic waves are subsequently transformed into electrical energy and displayed on the monitor.[7-9]

The fluctuation in image intensity is determined by the capacity of ultrasound waves to penetrate tissue. Bright or hyperechoic regions have more tissue density, whereas dark or hypoechoic regions have lower or no tissue density. Anechoic or black zones are areas of tissue where nearly no waves are reflected.[9] Wavelength affects image resolution. Higher frequencies result in shorter wavelengths, which improve resolution but reduce penetration. As a result, lower frequencies are required to visualize deeper structures in the skin.[7]

In general, routine imaging of the abdominal organs is performed using ultrasound waves in the frequency range of 3-5 MHz. Frequencies in

the range of 7.5-15 MHz are necessary for examination of more superficial structures (such as lymph nodes, testes, or thyroid gland).[10] Internal organs are visualized using low-frequency ultrasound, but HFUS, which is defined as ultrasound with a frequency of at least 20 MHz, has a substantially shallower tissue penetration depth. HFUS penetrates shallower yet generates higher resolution images of tissues and structures closer to the skin surface. The dermis and epidermis can be seen at frequencies between 20 MHz and 25 MHz, but only the epidermis can be seen at frequencies 50 MHz and higher.[11]

The most recent ultrasound technologies, ultra-high-frequency ultrasound (UHFUS) (frequency >30 MHz) and HFUS (frequency between 20-30 MHz), further enhance image clarity and broaden the variety of uses for ultrasound in dermatology. Ultrasound images are produced in real time with quick capture times, enabling physical modifications and the best possible imaging. Although HFUS and UHFUS waves have a difficult time passing through tissue, they can nonetheless produce shallower detail and greater resolution. Because of this, HFUS and UHFUS are perfect for seeing the skin and other superficial organs.[10] According to the Guidelines for Performing Dermatologic Ultrasound Examinations by the Dermatologic Ultrasound (DERMUS) group, dermatological analysis should use a minimum frequency of 15 MHz. The 15–22 MHz range is advised for visualizing deeper lesions due to the multifrequency nature of the available probes.[10] Skin examinations require linear transducers, broadband transducers, and high-frequency (≥ 15 MHz) transducers.[12]

The ultrasound image of normal skin corresponds to the layers observed in histological examination, therefore three layers can be differentiated with varied echogenicity.[13] The epidermis layer is mainly composed of keratin, is densely packed, and consists of fibrous protein structures that are strongly reflected by ultrasound waves. Thus, the epidermal layer appears as hyperechoic lines, and in some areas such as the acral area appears as bilaminar hyperechoic lines. The dermis layer includes a lot of collagen, therefore it seems hyperechoic but not as echogenic as the epidermis layer. A hypoechoic region, also known as the papillary dermis layer, may appear in the superficial dermis. The subcutaneous layer shows underneath the dermal bands as a network of hyperechoic lines linked to the septa. Hypoechoic areas within the septa depict fat lobules, allowing unhindered transit of ultrasound waves.[9,14]

The Role of HFUS in Skin Malignancy

HFUS is an objective, noninvasive examination method with the potential to be uses in the diagnosis and localisation of skin tumours. In principle, the utilization of HFUS in skin malignancies covers diagnosis, staging and treatment phases, and this method can be integrated into the assesment of suspected tumor cases. HFUS can provide information about tumour features such as size, shape, depth, consistency, and vascularity, which can be assessed before an invasive skin biopsy or surgery. This may reduce the need for excisional biopsies in clinically benign cases. This can reduce patient stress, functional impairment, material costs and specialty follow-up.[5,7,15]

HFUS helps define excision margins, enables earlier diagnosis, helps determine the effectiveness of therapy, and potentially prevents premature mortality in lesions with higher oncologic alertness. Another important application of HFUS is detecting skin malignancies that infiltrate relevant anatomical structures, particularly tumors in the head region. HFUS is available faster than Computed Tomography Scan (CT Scan) or Magnetic Resonance Imaging (MRI), but is similarly accurate in detecting calvarial metastasis.[15]

The neurovascular peritumoral structures can be mapped by preoperative HFUS to reduce surgical risk and enhance aesthetics. It can also help with vigorous treatment, lowering metastasis and recurrence rates. The most essential application is identifying preoperative skin cancer borders, excluding infiltrative lesions, and delineating tumour borders. This is particularly beneficial in detecting depth >/<1 mm and determining satellite, deep transit, or nodal metastases. Proper preoperative assessment of the tumor's extent can help

limit the size of surgical flaws. HFUS, on the other hand, can efficiently detect infiltration of relevant anatomical tissues such as fascia, muscle, cartilage, and bone cortex, allowing surgeons to take a more aggressive approach.[12,15,16]

This imaging technique is effective for visualising and studying sentinel lymph nodes in cases of malignant melanoma. HFUS is also an effective method to detect local tumour recurrence or lymph node recurrence during surgical follow-up evaluation, especially for tumours with a high chance of local recurrence or excised lesions with inadequate margins.[5,12]

HFUS is a supporting examination for clinical diagnosis and an effective noninvasive approach for planning the treatment of certain skin tumours. In addition, HFUS can assess prognosis in some cases that require additional management. The prognosis is assessed based on the predicted risk of recurrence, metastasis, and survival rate.[5,15]

The examination results of BCC and melanoma appear similar, in the form of hypoechoic circular or oval-shaped structures surrounded by hyperechoic areas. As a result, HFUS cannot be used for final tumour type diagnosis. Although some studies indicate that benign tumours and BCC display more internal echo than melanoma, it is also unable to distinguish between benign and malignant tumours on the ultrasonic pattern.[10] So it can be emphasized that HFUS is utilised as a solitary diagnostic method, but rather in conjunction with clinical examination and histopathological findings to guide in reaching a definitive diagnosis and treatment strategy.[7]

While it is not possible to distinguish between benign and malignant lesions with certainty, there are some things that can lead to suspicion of the type of lesion. Compound nevus is a frequent benign tumour that develops on the skin. Compound nevus shows an ultrasound image of a clearly demarcated hypoechoic mass lesion in the lower epidermis that extends into the dermis and causes a mass effect in the underlying dermis. The clear boundary features may help distinguish it from melanoma. Another example of a benign tumor is seborrheic keratosis. Seborrhoeic keratosis is a benign epidermal tumour that commonly affects middle-aged and elderly adults. Ultrasound imaging of seborrhoeic keratosis indicates a lesion that is a well-delimited mixed echogenic mass in the epidermis with entry echo epidermal thickening. The very sharp boundary between normal and abnormal tissue indicates the benign nature of these lesions.[5]

Color Doppler ultrasound, paired with spectral Doppler ultrasound, can indicate macrocirculation at the tumor's base. This can help distinguish between malignant and benign lesions. Hypervascularization, uneven blood flow model with peripheral or mixed distribution, increased blood velocity, and many vascular pedicles are some of the vascular signs that can signal malignant lesions.[17]

Another limitation of the HFUS modality in skin malignancies is that it cannot provide tissue diagnosis. HFUS cannot distinguish between tumor and inflammatory infiltrates, which may result in overestimation of tumor dimensions.[5] Many studies have shown that HFUS shows an overestimation of lesion thickness, but the results obtained are still within the level of accuracy that is useful for assessing lesions before surgery.[18] In addition, HFUS devices may be costly. The use of HFUS also requires specialized medical training of doctors. Dermatology ultrasound experts should be skilled in skin pathology to link HFUS images, physical examination, and histopathology. [15]

Basal Cell Carcinoma (BCC)

In general, HFUS shows BCC as oval or slightly irregular hypoechoic lesions with clear borders and hyperechoic areas showing microcalcifications, corneal cysts, or nests of apoptotic cells with a "cotton flower" appearance. Morphiform or micronodular BCC is characterised by the presence of at least seven hyperechoic spots, which suggests a high probability of recurrence. BCC may be associated with low-flow blood vessels within or at the base of the tumour. A characteristic feature of BCC is that the sebaceous glands appear isoechoic, showing a blurred tumor picture and peritumoral inflammation with an angle at the

base. This increases the thickness of the tumor measured by HFUS.[15]

Nodular type BCC is a type of BCC that can reach penetration into the deep dermis layer. BCC has a picture of HFUS hypoechoic nodules in the skin or subcutaneous tissue. Hypoechoic nodules may appear irregular, circular, oval, ribbon-like or seed beads. Ultrasound characteristics of BCC can have well-defined borders or ill-defined borders, hyperechoic spots with homogeneous or heterogenous internal echo, and hyperechoic spots. On posterior echo some lesions show obvious posterior echo changes, posterior acoustic shadow artifacts, or show posterior enhancement artifacts (Figure 2).[19-21]

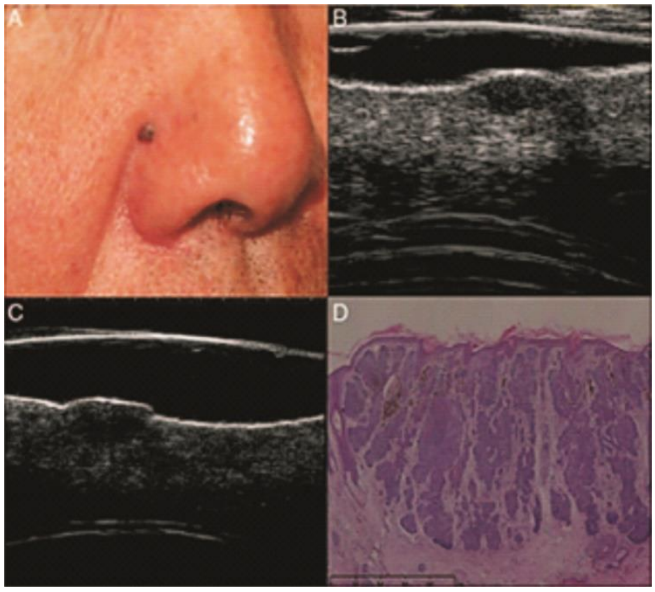

Figure 1: *Nodular type BCC: A. Clinical picture of a hyperpigmented nodule in the right nasolabial fold; B. 20 MHz HFUS image and C. 50 MHz HFUS images obtained hypoechoic dermal lesions with firm boundaries, oval shape, homogeneous, and several hyperechoic points; D. Histopathologic features of dermal nodular type BCC.[21]*

Superficial type BCC appears similar to nodular BCC on HFUS but with a flat shape instead of an oval shape. The picture of superficial type BCC presents with a well-defined lesion, a band-like hyperechoic zone, no hyperechoic dots, and no internal echo and posterior acoustic artifacts (Figure 3).[21,22]

Nodular type and superficial type BCC are low risk BCC. High-risk BCC subtypes, that are micronodular, basosquamous, infiltrative, and mixed types, have similar features to low-risk BCC. However, some types of high-risk BCC have a more irregular shape and deeper lesion depth extending into the subcutaneous layer. In high- risk BCC lesions, dense hyperechoic dots are more common, such as in the micronodular and morphea form variants.[12,21,23]

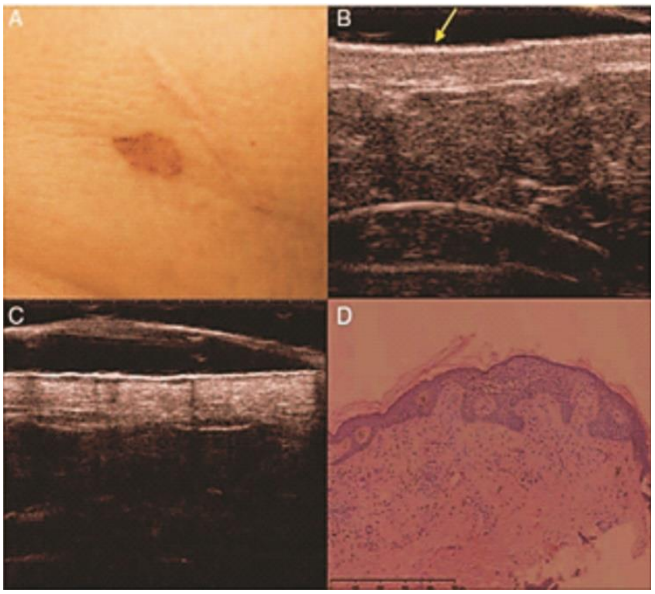

Figure 2: *Superficial type of BCC: A. Clinical picture obtained irregular hyperpigmented patches in the abdomen; B. HFUS 20 MHz image obtained epidermis with indistinct boundaries and upper dermis slightly hypoechoic band-like thickening; C. HFUS 50 MHz image obtained epidermis and epidermal thickening with epidermal undulations and hypoechoic dermal zone shaped like a band, not obtained without hyperechoic dots with internal or posterior echoe; D. Histopathologic picture of nodular type BCC.[21]*

Squamous Cell Carcinoma (SCC)

SCC typically involves deeper layers and manifests as heterogeneous hypoechoic lesions with irregular margins and no hyperechoic spots on HFUS (Figure 4). The thickness or depth of invasion is a key predictor of metastasis, so the lesion should be monitores during its progression. Lymph node evaluation is essential in SCC to detect locoregional metastases, and ultrasound of the liver and regional lymph nodes can be performed simultaneously. In contrast to BCC, where neovascularisation is less noticeable and fre-

quently at the base of the lesion, the vascular pattern increases diffusely throughout the mass, as visualized using Doppler ultrasound ultrasound.[12,24]

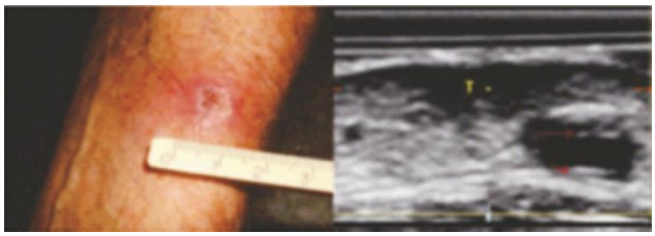

Figure 3: *Images of SCC in HFUS. The T indicates a hypoechoic mass located 2 mm from the vein. The red arrow shows venous valve as a straight white structure.*[5]

HFUS examination of nodular type SCC shows distinct nodular hypoechoic mass lesions in the epidermis, subepidermal area, and upper dermis. Invasion into the dermis distinguishes it from Bowen's disease (Figure 5).[5]

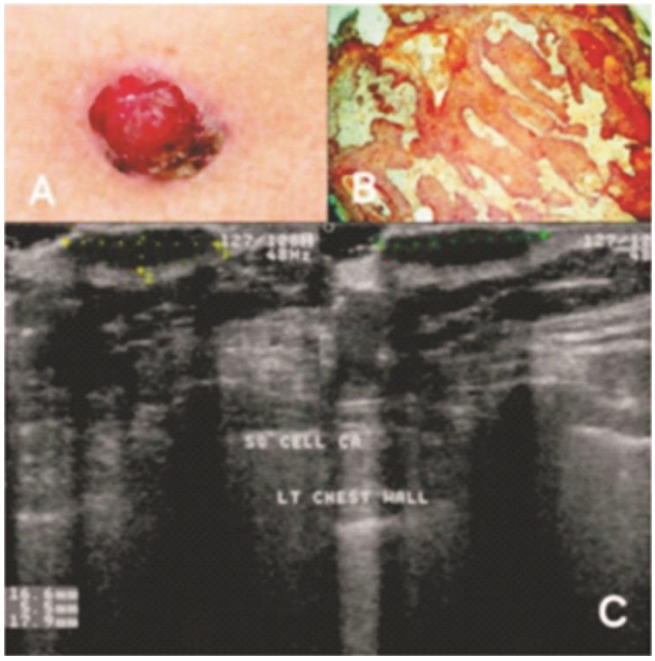

Figure 4: *Nodule form of SCC. A. Clinical features of KSS: a single plaque with ulcer and crusts on the lateral chest wall. B. Histopathologic features: Pseudoepithelioma hyperplasia, horn pearls, double mitosis and well-differentiated squamous cell collections in the dermis (HE stain, ×100). C. HFUS examination: clear nodular hypoechoic mass lesions in the epidermis, subepidermal area, and upper dermis.*[5]

The appearance of intralesional hyperechoic dots in BCC is a significant discriminator to distinguish between high-risk BCC and SCC. In addition, several investigations have found that hyperechoic dots are an essential imaging marker in the diagnosis of BCC, as more hyperechoic dots would indicate a higher risk. Hyperechoic dots usually do not show posterior acoustic shadows.[25]

Thickened hyperechoic lines on the lesion surface accompanied by posterior acoustic shadows are common findings of SCC on HFUS examination. Keratotic scales or crusts on the lesion surface cause the thicker hyperechoic line and posterior acoustic shadow. In addition, it was found that SCC showed less heterogeneous echogenicity than high-risk BCC. Acoustic shadows caused by hyperkeratinization may mask the interior features of SCC lesions. External variables can easily modify the lesion surface, which does not adequately reflect the interior expression of the lesion. Therefore, echogenicity and homogeneous lesion surface are not reliable indicators for differentiate SCC and high-risk BCC.[25]

Evaluation of SCC lesions with HFUS or postoperative follow-up and lymph nodes structures around the lesion is recommended in cases of recurrent SCC, poorly differentiated tumors, lesion diameter greater than 2 cm or thicker than 2 mm, invading nerves, blood vessels, lymphatic pathways, and high-risk anatomical locations, such as on the lips, ears, and perineum. HFUS will describe SCC as heterogeneous tumors that are irregular, fully hypoechoic, and tend to invade deeper tissues.[15]

Melanoma

HFUS cannot detect pigments such as melanin but allows noninvasive evaluation of the primary tumor. HFUS can detect primary tumor characteristics, such as thickness and blood flow, which may contribute to modifications in melanoma management. It can already help calculate the Breslow index in a substantial proportion of patients with melanoma. HFUS can aid in identifying difficult-to-define lesion borders, as well as determine the thickness or depth of lesion invasion.[18,26,27]

On HFUS examination, melanoma lesions appear as fusiform, well-demarcated lesions with little echo. Melanomas generally appear as hypo-echoic, homogeneous areas that are easily distinguishable from the surrounding tissue. HFUS describes melanoma as a hypoechoic, heterogenous, oval or oblong lesion, well demarcated by a hyperechoic epidermis. The epidermis may be uneven or discontinuous in ulcerated malignancies. Except for ulcerated melanomas, a hyperechoic epidermal line is typically visible above the tumour. Acoustic transmission is frequently increased. The correlation between sonographic and histological thickness has been observed to be excellent. However, peritumoral inflammatory infiltrates may be observed in HFUS, increasing the chance of an erroneous tumour depth measurement. Satellite and in-transit nodules seem strongly hypoechoic, moderately homogeneous, and well-defined within the dermis or hypodermis (Figure 6).[12,15,18,24]

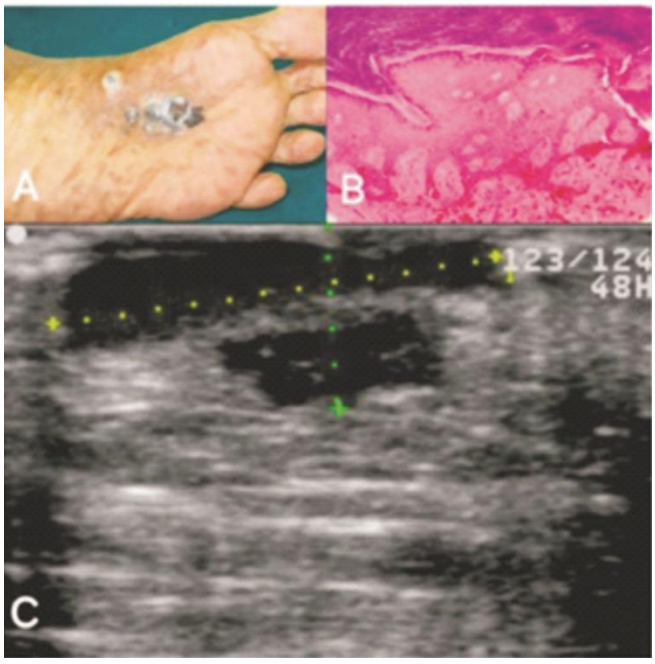

Figure 5: *Melanoma of the skin. A. Clinical picture of multiple hyperpigmented nodule lesions on the plantar pedis. B. Histopathology showed dense hyperkeratosis with dispersed infiltration of the dermis with atypical melanosis. C. HFUS lesions are hypoechoic nodules located in the subepidermal, dermal, and subcutaneous tissues.*[5]

Primary cutaneous melanoma generally appears hypervascular on HFUS examination compared to nevus features. Vascular flow signals may be difficult or impossible to detect in very thin lesions. Vascular flow signals are more easily detected in lesions thicker than 2 mm. Melanoma has hypervascularity because of its angiogenic potential. The level of tumour vascularization correlates with the risk of locoregional lymph node metastases, patient prognosis, and patient survival rates.[5,12,15,24]

Melanoma can be differentiated from benign melanocyte growth with a specificity as low as 30%. The use of colour Doppler ultrasound significantly improves diagnostics accuracy. Melanomas show the presence of denser vascularization compared to benign nevi, which often show low-flow arterioles. Another study on pigmented lesions discovered that monitoring of blood flow direction within the lesion achieved 100% specificity in identifying melanoma from nonmelanoma tumours.[9]

Doppler ultrasound is useful in evaluating cutaneous melanoma, as it can demonstrate that identifying new blood vessel formation using ultrasound can predict how likely melanoma is to spread. In a study using Doppler ultrasound flowmetry (10 MHz) in melanoma, it was discovered that enhanced blood vessel development and higher peak systolic frequency were better predictors of survival after 15 years.[14]

Conclusion

HFUS can help evaluate lesion characteristics, thereby improving diagnostic accuracy, reducing the need for biopsy, and aiding excision planning by defining excision margins in skin malignancies. HFUS cannot be utilised as a solitary diagnostic tool. Current diagnostic techniques use HFUS in conjunction with clinical examination and histopathological results to guide the clinician in reaching a definitive diagnosis and therapy strategy. A key limitation of HFUS is its inability to reliably distinguish between benign and malignant lesions with certainty and its inability to provide tissue-level diagnostics. Colour Doppler ultrasound exa-

mination paired with spectral Doppler ultrasound can detect macrocirculation at the base of the tumour which may help differentiated malignant from benign lesions.

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Author's Contribution

FS, MYL: Contributes to conception of innovation, data analysis, data interpretation and manuscript writing.

MS: Contributes to data analysis and data interpretation.

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