High-Frequency Ultrasound (HFUS) in the Management of Skin Cancer Treated with Cryosurgery

13

Paola Pasquali

Contents

Key Points

- High-frequency ultrasound (22 MHz) of skin malignancies gives information on volume and shape to help select the best treatment.
- HFUS identifies BCC with more than one histologic subtype, especially when there is a need to identify nodular elements within a clinically superficial tumor.
- Multiple BCC patients will benefit from a previous HFUS of all lesions before deciding treatment upon an approach or cryosurgical technique.
- Trans-cryosurgical HFUS enables visualization of the depth obtained by the freezing front.

13.1 Introduction

Until a few decades ago, dermatologists had based, and in some cases still base, most of their diagnoses on simple clinical evaluations. Fortunately, techniques and digital imaging have become available in user-friendly formats. Compact, less expensive equipment has come to market, and less invasive technologies have been developed. Today, imaging is used in diagnosis, treatment evaluation, and post-therapeutic control. In malignant tumor management, it is not feasible to biopsy every single lesion, particularly in those patients with multiple

P. Pasquali, MD
Department of Dermatology, Pius Hospital de Valls, 43800 Tarragona, Spain
e-mail: pasqualipaola@gmail.com

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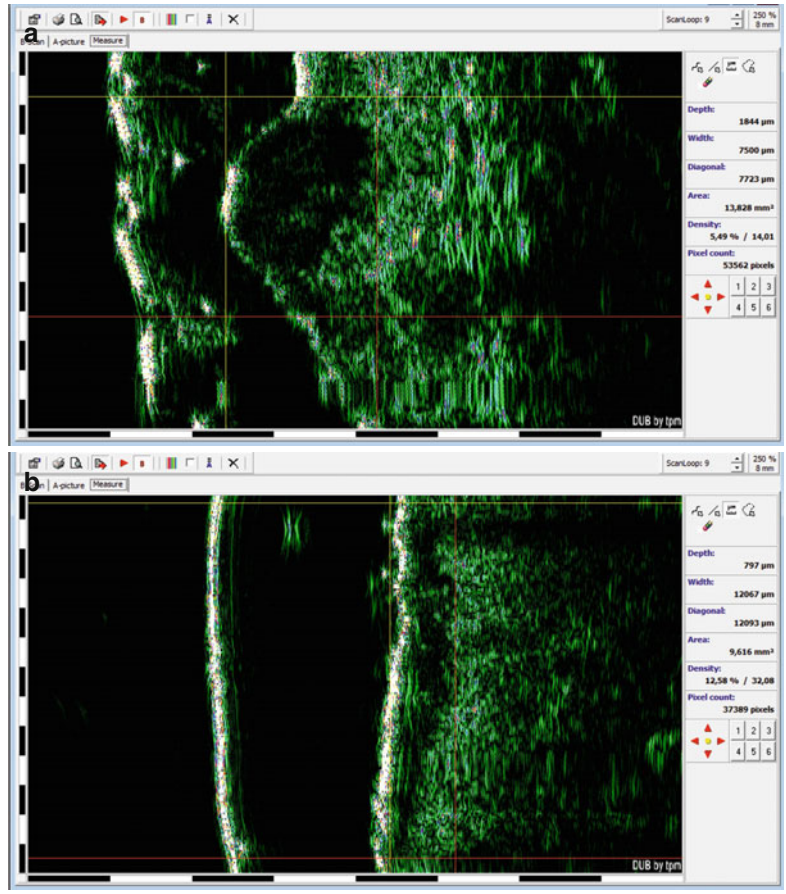


Fig. 13.1 (**a**) HFUS of a nodular BCC (size: 1,844 mm depth × 7,500 mm width; (**b**) HFUS of a superficial BCC (0,797 mm depth × 12,067 mm width

lesions (such as basal cell carcinomas); therefore, clinical evaluation will necessarily support itself with imaging technology in order to obtain the correct diagnosis [1].

Dermoscopy has become immensely popular and stands as an indispensable tool to uncover clinically invisible morphological aspects of skin lesions. On the other end of the spectrum of the noninvasive tools for diagnosing skin lesions one finds reflectance confocal microscopy which will identify cellular structures to a resolution similar to histology. It still has not gained the place it deserves in daily practice probably due to its high cost and need for formal training to interpret its images.

In the middle of this spectrum stands high-frequency ultrasound (HFUS). It is a noninvasive technique capable of complementing tumor information not obtainable by the aforementioned methods [2, 3]. It is a small, portable piece of equipment, easy to carry and use. Its cost is intermediate, between dermoscopy and confocal microscopy; it requires training for image interpretation.

HFUS allows visualizing shape as well as measuring the length, depth, and width of skin tumors (Fig. 13.1a, b). The 22–50 MHz applicators are the most commonly used in dermatology and ideal for those lesions less than 12 mm in length and 6–8 mm in depth.

It seems inconceivable today to examine the skin without the aid of a dermoscope; soon, high-frequency ultrasound (HFUS/HRUS, high-resolution ultrasound, high-resolution echography) should be included in the indispensable armamentarium of those actively working on skin cancer. For some, this has been a common practice for many years [4]. Combining noninvasive techniques (dermoscopy, HFUS, confocal) will save time and money as well as unnecessary biopsies.

The more information is available on a particular tumor, the better treatment can be provided. Clinical evaluation and dermoscopy will give information on the superficial morphologic aspects, HFUS will provide information on shape and volume [5, 6], and confocal microscopy will provide information on cellular aspects [7] (Fig. 13.2a–d).

There is an excellent correlation between dermoscopy and HFUS dimensions [5]. This means that the dimensions obtained by dermoscopy correspond to the HFUS length of the tumor. Therefore, the dermoscopy image corresponds to the real size of the tumor; however, only through HFUS one will know the actual depth and shape of the tumor.

Some tumor characteristics that can be better understood by HFUS evaluation are:

- *Volume/Shape*. The shape and size of a tumor can provide information of the type of tumor. Most BCC are anechoic and have a roughly elliptical shape; occasionally, they are elongated anechoic and have a collar necklace or rosary pattern (Fig. 13.3). SCC are also hypoechoic, but a thick superficial crust needs to be removed before visualization [4]. They are usually thick lesions with irregular "iceberg" shapes. HFUS imaging will be of great help in choosing the proper site for biopsy or selecting the best method for tumor removal. In addition, some tumors have an iceberg shape: they appear small at the surface while the length underneath the surface is larger. This could be the cause of positive margins after surgery.
- *Depth*. The knowledge of the depth of tumors helps in deciding the correct surgical technique. For example, superficial BCC lesions can be diagnosed by clinical/dermoscopy [8] examination. Treatment options include cryosurgery, topical immunomodulators like imiquimod, photodynamic therapy (PDT), and curettage/electrocoagulation, among others. There is no need for costly, lengthy, expensive, and invasive techniques like Mohs micrographic surgery on a superficial carcinoma. Although this seems logical, the out-of-proportion use of Mohs surgery (1 out of every 4 tumors are treated with MMS [9]) suggests that this technique is being used for treating many superficial lesions. The HFUS image of a superficial BCC shows a hypoechoic elliptical area(s) of less than 1 mm of depth. Individually, each island of tumor measures 1–1.2 mm in depth. Lengthwise, they can be small (1–2 mm) but can also be quite large, requiring a segmental HFUS evaluation in order to cover the whole area. HFUS allows the determination as to whether BCC is only superficial or it has a deeper component within the tumor. Apparently "superficial BCC" can "hide" nodular or even morpheaform elements (admixture tumor), as is the case in roughly one-third of all BCC [10, 11] (Fig. 13.4a, b). The latter is a common cause of treatment failure and recurrence (Fig. 13.5). Sometimes this reoccurrence is many years later. The tumor's depth has to be determined throughout the whole tumor area using HFUS readings. The deep margin evaluation by HFUS is limited to tumors under 8 mm in depth. Proper selection of the biopsy site is of utmost importance [12]; therefore, HFUS-guided biopsy could be another possible indication.
- *Length*. The longitudinal/width margin evaluation by HFUS is limited to tumors under 12 mm. For large lesions, HFUS might need to be performed by sectors.

13.2 HFUS and Cryosurgery

The combination of HFUS and cryosurgery has the following advantages:

1. This combination gives the surgeon information regarding the volume, depth, and length of the tumor.
2. This combination allows for visualization of the depth of the freezing front.

13.3 HFUS Volume and Cryosurgery

Cancer cells need a temperature of at least – 50 °C to be destroyed. That temperature must be reached throughout the entire tumor including the safety margin of 4 mm. The temperature at

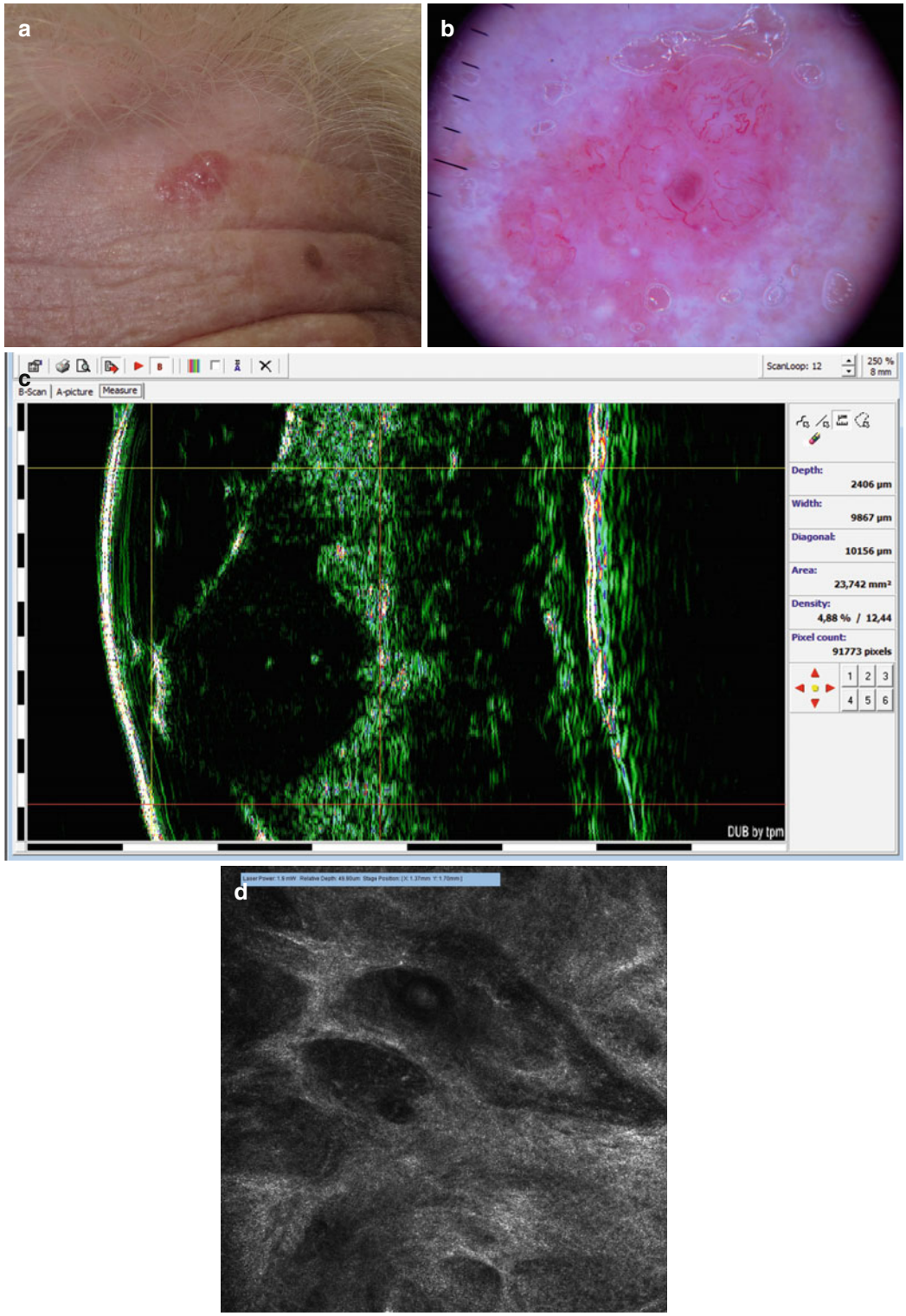


Fig. 13.2 (**a**–**d**) Four ways of looking at a nodular BCC: (**a**) clinical photograph, (**b**) dermoscopic image, (**c**) HFUS, (**d**) confocal microcopy (**d**: Courtesy of Rainer Hofmann-Wellenhof, MD)

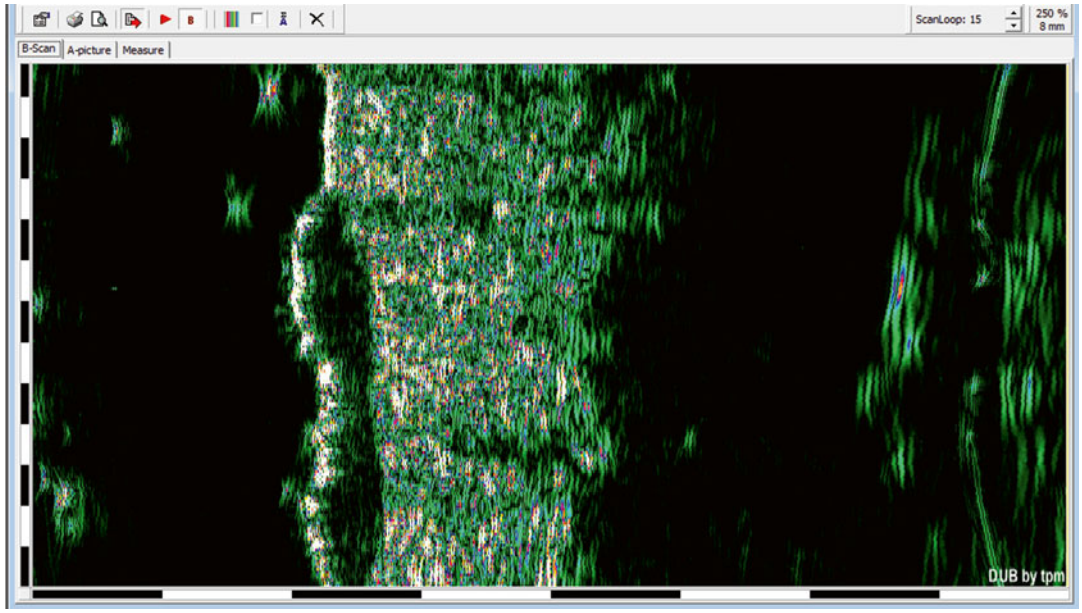


Fig. 13.3 Collar necklace HFUS image of a superficial BCC

the center of the freezing ball is the first to achieve the optimal killing temperatures. The concern is at the periphery of the tumor where suboptimal freezing temperatures might leave undestroyed malignant cells. Therefore, temperature needs to be measured at the periphery. Following the isotherm, the temperature at the depth of the tumor can be inferred (Fig. 13.6).

Deep tumors are best treated with close (probe) or chamber technique because a greater depth is reached (Fig. 13.7). In general, the length/depth ratio is 6×1 (for nodular BCC the ratio is 4×1) [5]. Superficial/shallow tumors can be treated both by open (spray) or close (probe) technique.

13.4 Multiple BCC Management and HFUS

Management of syndromic and non-syndromic multiple BCC represents a real challenge. No one treatment alternative is sufficient, and multidisciplinary approach/combination treatments are usually required. One of the problems is

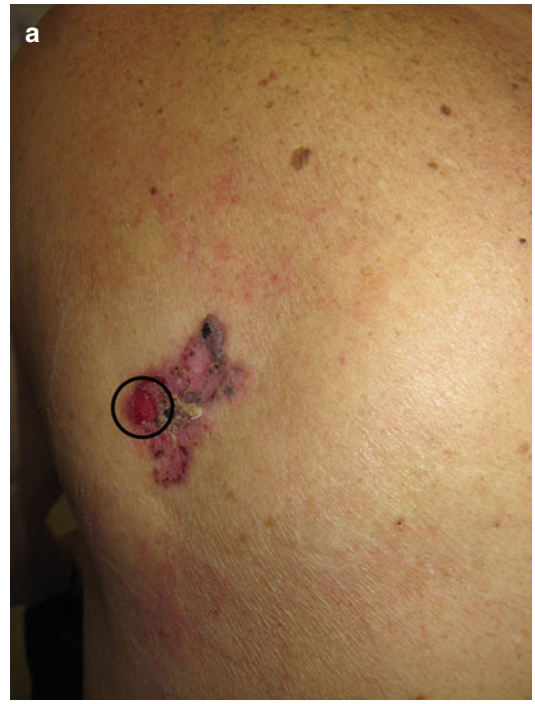


Fig. 13.4 (**a**, **b**) A very large pigmented BCC on the back. (**a**) Clinical evaluation and dermoscopy showed a superficial BCC with an ulcerated area (*circle*). (**b**) HFUS showed a nodular area

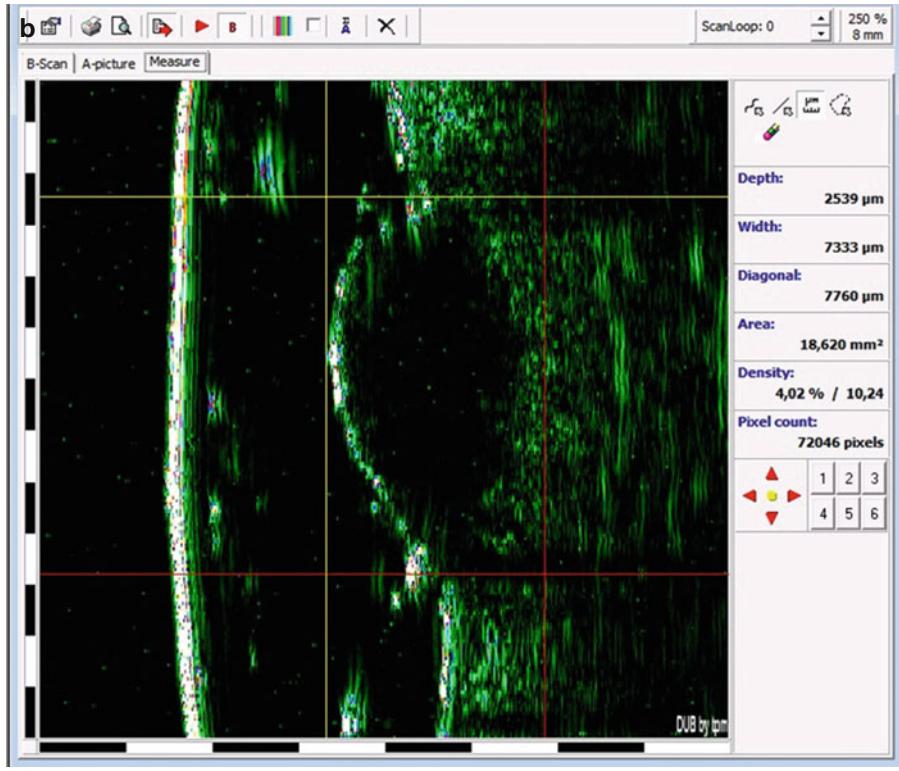


Fig. 13.4 (continued)

that the complete genetics involved in the genesis of these tumors is still not fully understood, especially in non-syndromic cases [13]. Genetically induced BCC includes conditions like Gorlin, Bazex-Dupré-Christol, and Rombo syndrome as well as xeroderma pigmentosum. Other disorders that can be associated with multiple early onset skin malignancies include those with defects in DNA replication/repair functions, genodermatoses affecting folliculosebaceous unit, immune response, and melanin biosynthesis [14].

Many treatment modalities have been proposed that range from topical and oral treatments, PDT, surgical excision, cryosurgery, Mohs micrographic surgery (MMS), to ablative lasers. It is advisable to excise aggressive lesions and reserve skin preserving alternatives for the rest [15]. For multiple BCC patients, an algorithm suggests the workup recommended (Fig. 13.8), indicating the most common skin-sparing modalities [16] and deep tumor removal modalities (Table 13.1).

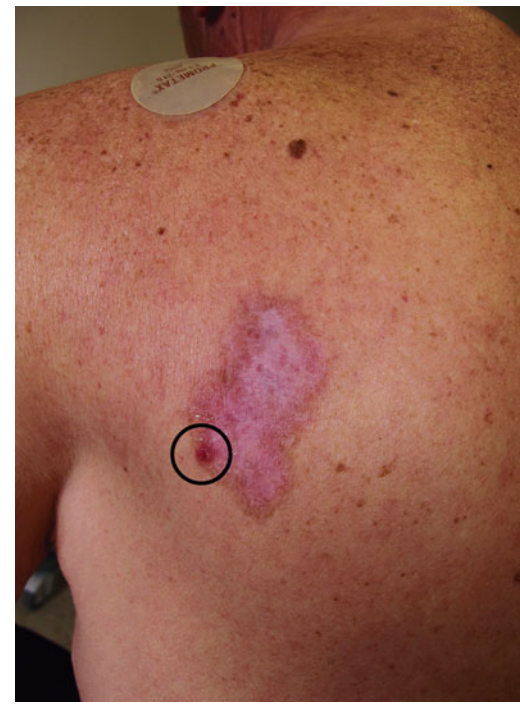


Fig. 13.5 Same patient as in Fig. 13.4. BCC was treated with topical imiquimod treatment. After healing from the imiquimod treatment, there was residual tumor (corresponding to the nodular part). This residual tumor was later treated with cryosurgery (close technique)

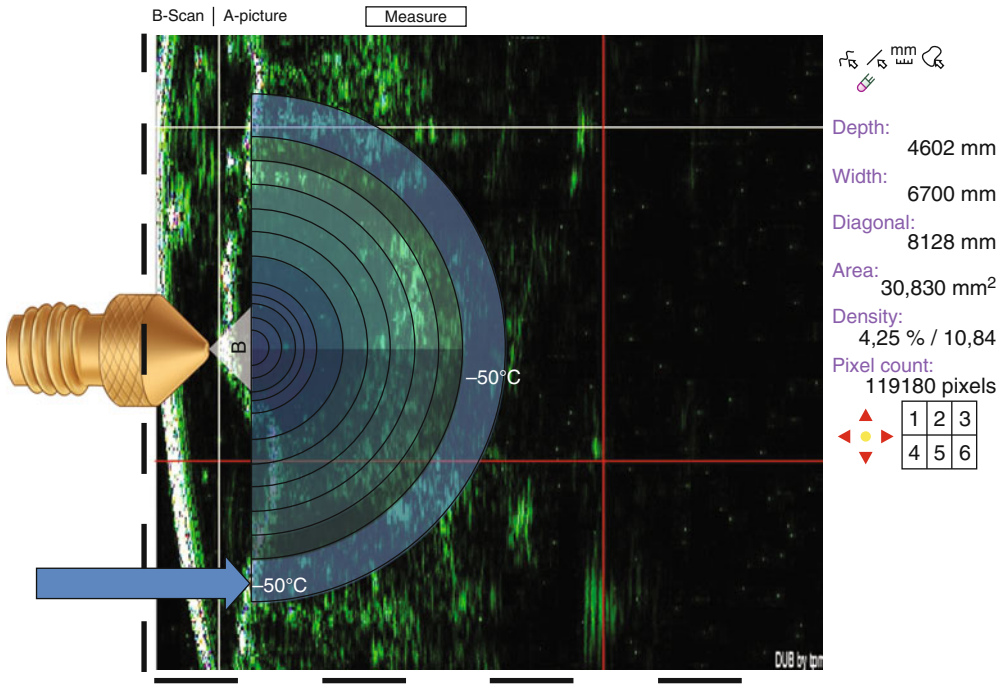


Fig. 13.6 The ice ball expands in a roughly hemispherical shape. The temperature decreases from the center out in isotherm. The lateral spread from the edge of a probe is approximately equal to the depth of the freeze. The temperatures at the base and at the lateral margin are the same

In multiple BCC patients, a previous HFUS map of the lesions should be performed to choose the best treatment option (Fig. 13.9).

Cryosurgery can be the treatment of choice for both superficial or deep tumors. In both cases, the following concepts are of utmost importance:

- *Temperature*. Keep always in mind the required −50 °C needed to kill a skin cancer cell regardless of tumor depth.
- *Depth*. For deep tumor, it is best to choose the close (probe) technique because the freezing is faster and deeper (covered area of ice ball per minute) as well as more precise (freezing is restrained to the probe or chamber area). For shallow small tumors, open (spray) technique is probably better to reduce damage to deep structures; for deep small tumors, probe cryosurgery is the best but not the sole choice.
- *Spray vs Probe*. Lower temperatures are achieved faster with metal probes. If the correct size probe is available, the close technique will be the best choice.

13.5 Monitoring with HFUS: Trans-cryosurgical HFUS

The distribution of temperature in isothermal areas lets one infer the temperature in hidden parts of the tumor. The combination of HFUS and cryosurgery performed with devices that measure the temperature turns conventional cryosurgery into a non-blinded procedure.

Skin temperature monitoring by infrared sensing spares the use of thermocouple needles. The latter implies invasiveness from needle introduction which was performed mostly blinded (non-US guided).

Once freezing of the tumor has been performed by any chosen cryosurgical technique, the immediate HFUS image is black. This is because US waves are reflected by ice. Once thawing begins (from the surface of the skin down), the superficial part of the tumor becomes evident and, in time (starting from the top down), the whole tumor can be seen (Fig. 13.10a–c).

After the first freezing cycle, the area will be more hypogenic and the tumor larger. This is due

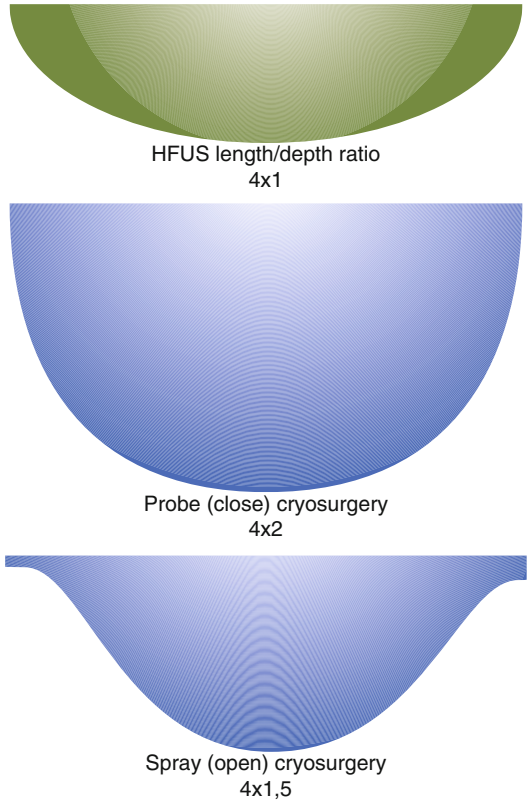


Fig. 13.7 The volume ratio of most nodular BCC measured by HFUS is 4 × 1. The ice ball of a close (probe) cryosurgery is approximately 4 × 2; for spray, cryosurgery has a hat shape, and it is approximately 4 × 1.5 (these last two shapes were obtained from a gelatin model)

to post-cryosurgery edema. After the second freeze-thaw cycle, this edema is even more apparent (Fig. 13.11a–c).

The depth of the freezing front can be visualized with HFUS, and the total thawing time can be measured. The skin temperature at the periphery of the tumor can be measured by infrared technology and the temperature at the bottom of the tumor inferred by isotherm temperature distribution. The previous knowledge of the tumor depth will allow the operator to know if the entirety of the tumor has been frozen at the correct temperature.

Essential Tidbits

- Measure BCC before deciding upon the best treatment option. Knowing the tumor volume will help avoid under- or overtreatment.
- HFUS is ideal for multiple BCC patients.
- Trans-cryosurgery HFUS gives an additional record of thaw time as well as visualizing depth of freezing front.

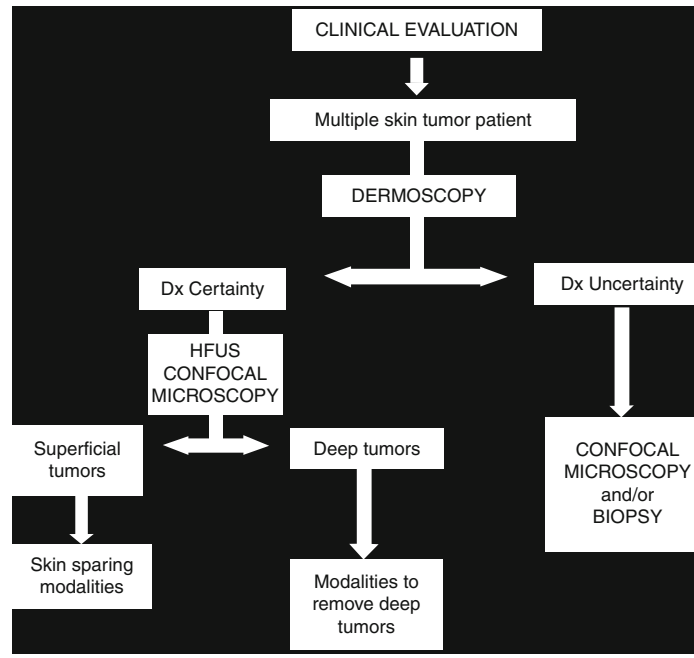


Fig. 13.8 Suggested algorithm for multiple NMSC patients

Conclusions

HFUS gives complementary information to other noninvasive techniques like dermoscopy and confocal microscopy. Further studies will help determine the relationship between shape/volume and histologic type and aid in the development of criteria to diagnose tumor subtypes. Incorporating this noninvasive technique into daily practice will help to select the best treatment modality for each tumor. The appropriateness of selection will reduce the chances of undertreating a tumor (by using a superficial treatment modality on a deep tumor) or overtreating [17] (by using, for instance, MMS in a superficial or small nodular BCC). In both situations (under- and overtreatment), the consequences can be dramatic. With under-treatment, leaving a residual a residual tumor growing under the skin surface freely for years can result in the tumor becoming inoperable or metastatic. Appropriate use criteria will avoid this scenario.

Table 13.1 Most common skin-sparing and deep tumor removal modalitites

Skin-sparing modalities
Topical treatment: imiquimod, 5 FU
PDT
Electrocoagulation/curettage
Shaving
Intralesional agents: 5 FU, methotrexate, bleomycin, IFN alpha (α)-2, IFN α-2a, IFN α-2b
Cryosurgery
Electrochemotherapy
Deep tumor removal modalities
Surgery
Mohs micrographic surgery
Cryosurgery
Electrochemotherapy

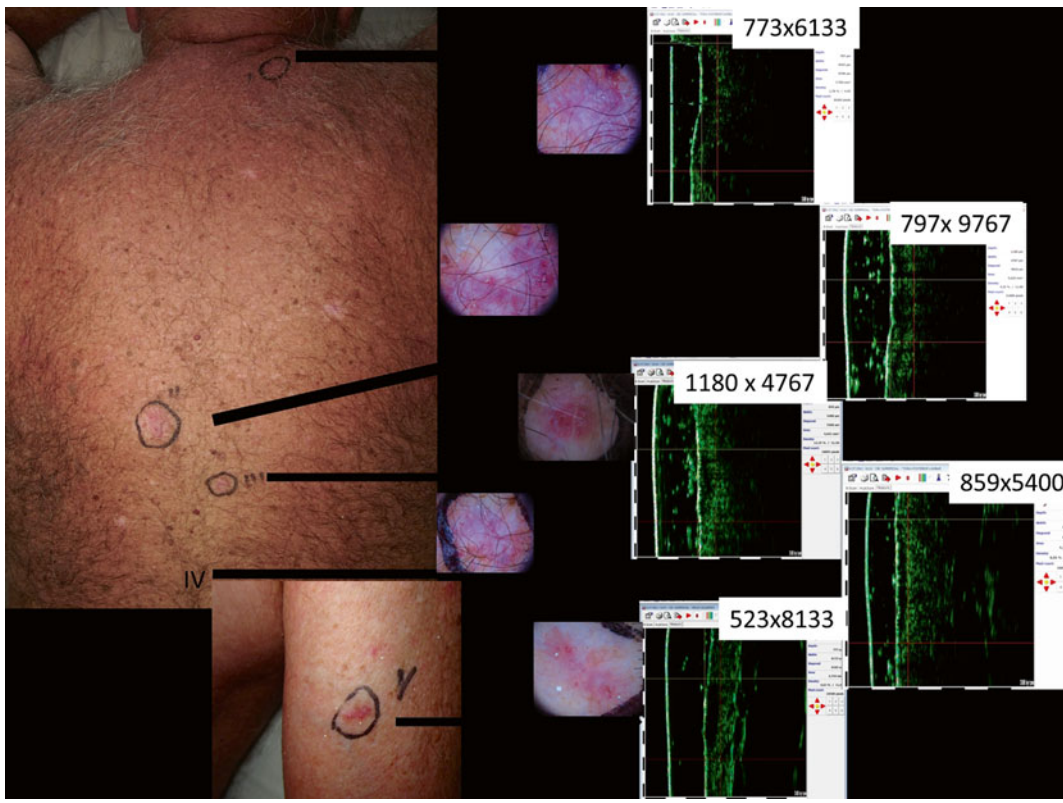


Fig. 13.9 Mapping a patient with multiple BCC. HFUS shows that all lesions are superficial BCC and can be safely treated with skin-sparing modalities

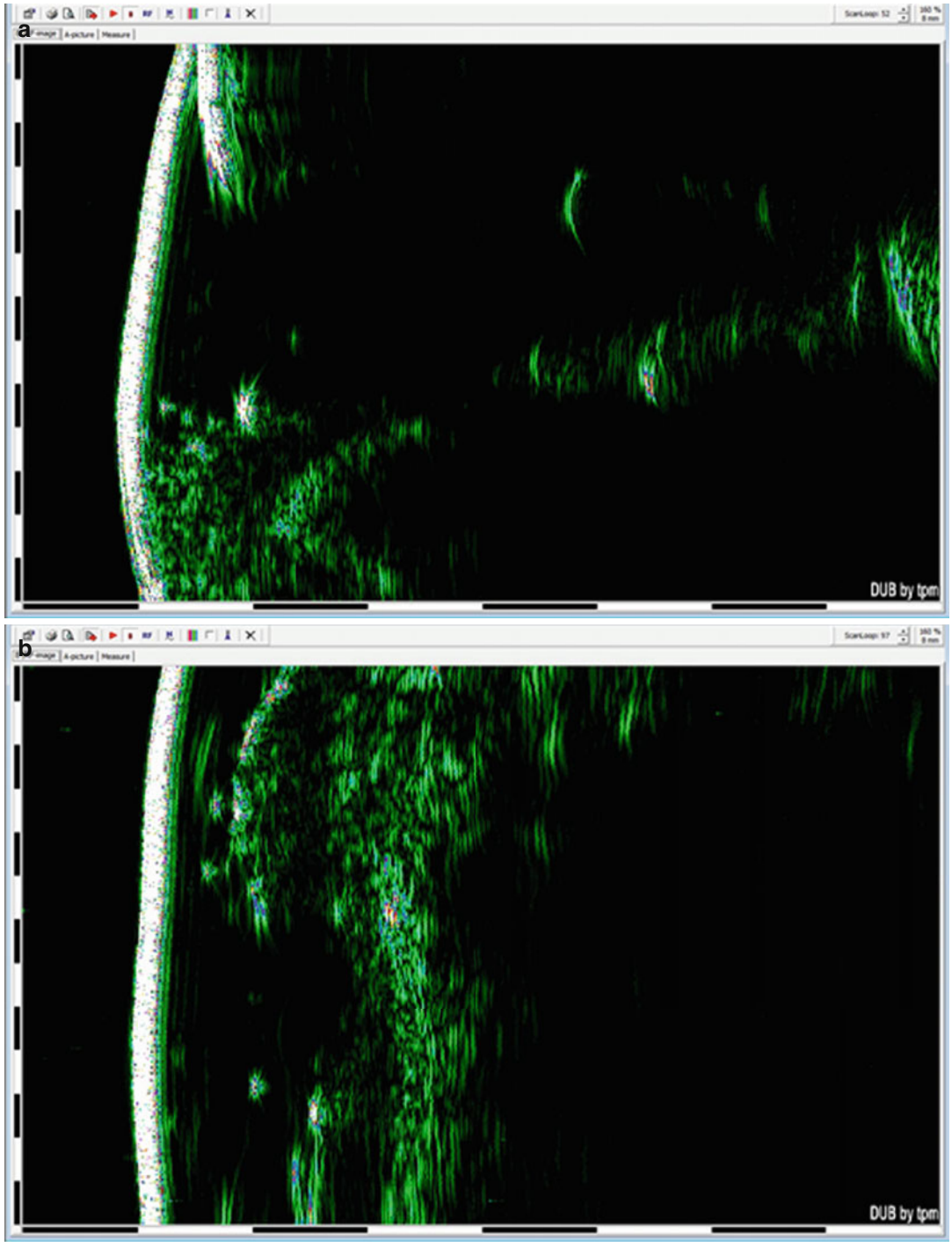
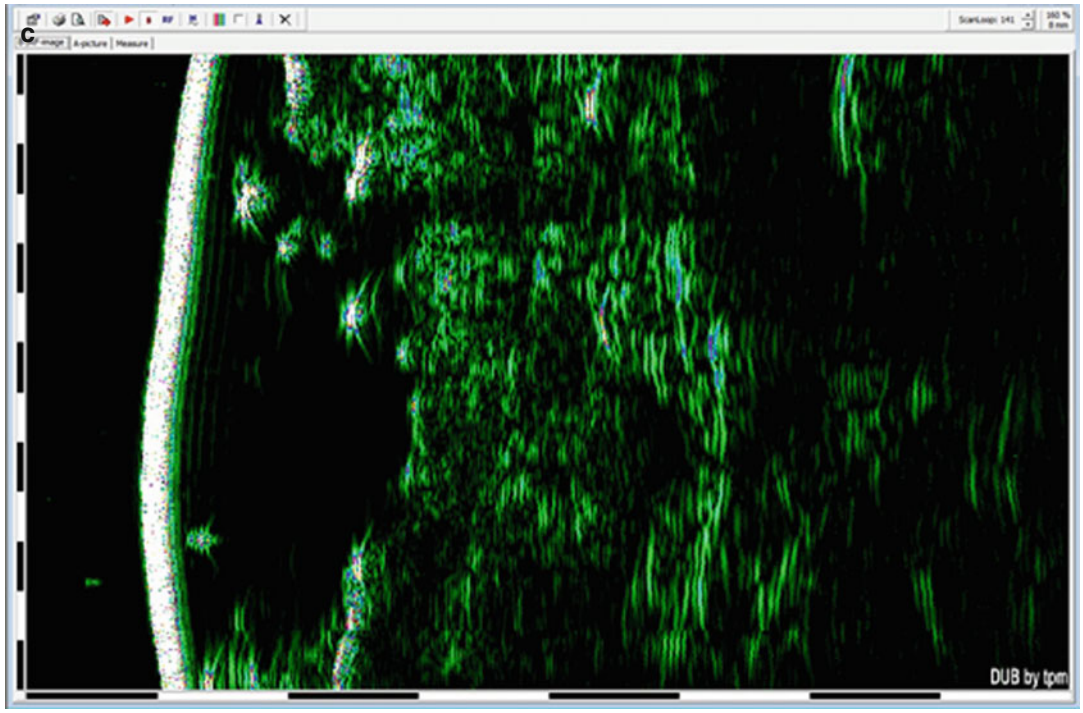


Fig. 13.10 (**a**–**c**) A BCC partially removed by deep shaving and treated with cryosurgery. (**a**) HFUS immediately after freezing showing a black area corresponding to the ice ball; (**b**) As thawing sets in, the superficial part becomes evident first and (**c**) the deeper component becomes apparent with complete thawing



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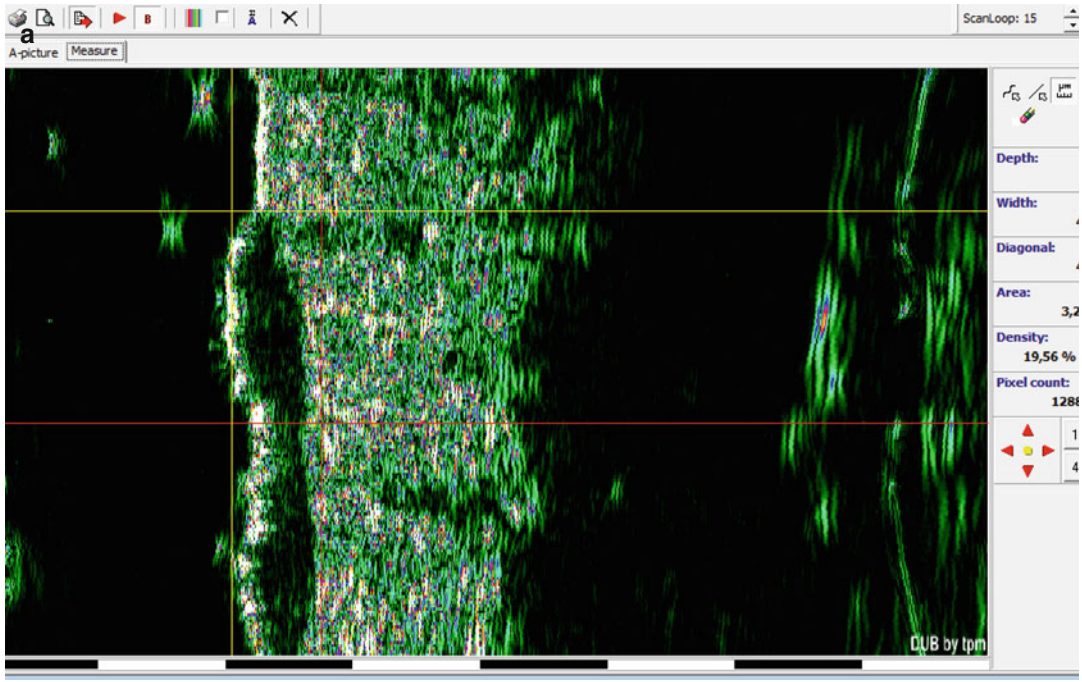

Fig. 13.11 (**a**) Superficial BCC. A small island is measured before treatment (total area: 3,294 mm^2). (**b**) First freeze-thaw cycle showing edematous tissue with slight increase in total area (3,798 mm^2). (**c**) After second freeze-thaw cycle (5,205 mm^2) showing an important local edema

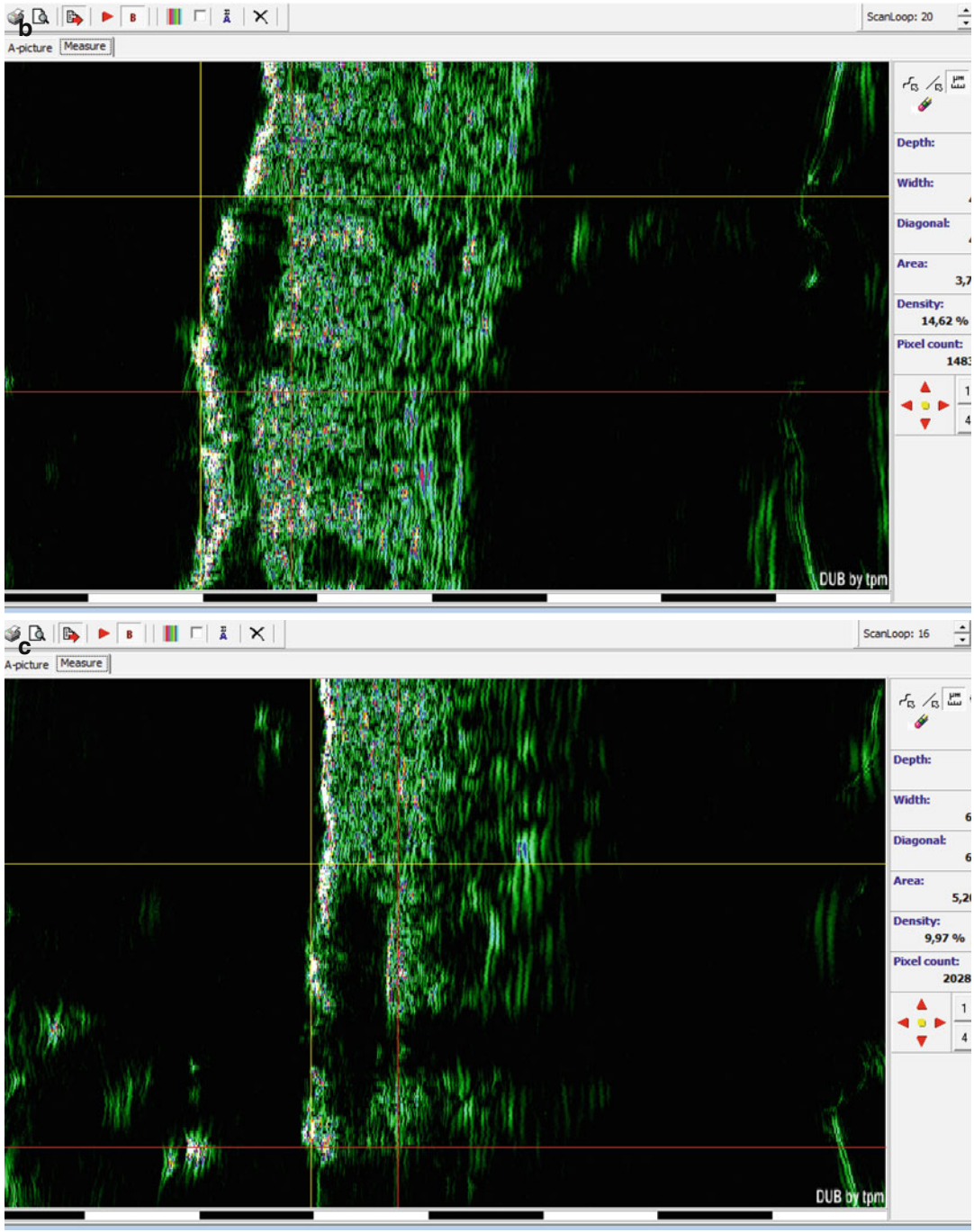

Fig. 13.11 (continued)

Glossary

HFUS	High-frequency ultrasound
MMS	Mohs micrographic surgery
Trans-Cryosurgical HFUS	Consists in doing an HFUS immediately after freezing, with the tissue still frozen

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