Use of Ultrasound in Cryosurgical Treatment

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Introduction

Keratinocyte carcinomas (KC) are the most common malignancy occurring in Caucasians, with numbers rising yearly worldwide, with the most frequent type being basal cell carcinomas (BCC). Possible factors driving this phenomenon are increases in both acute and prolonged UV exposure together with growing numbers of older people in the population, as these tumors are mostly prevalent in the elderly [1].

Indeed, the estimate global life expectancy is higher than ever: since 1900, it has more than doubled and is now above 70 years [2]. With longevity, the total number of malignant tumors is increasing, while the specialists required to treat them are being reduced in numbers [3]. As the incidence of KC increases, more, better, and less expensive treatment options are needed as the actual disease economic burden stands among the top [4].

Minimally invasive treatment for low-risk BCC includes surgical removal by destructive methods (such as cryosurgery and curettage/electrocoagulation) and nonsurgical modalities (such as photodynamic therapy (PDT) and topical treatments like imiquimod and 5-fluorouracil). These options might be used for low-risk BCC when surgery is contraindicated or impractical [5]. The drawback of these methods is the lack of histologic control of tumor removal and therefore they are considered "blind" methods.

Noninvasive imaging techniques (NIIT) are essential to diagnose skin cancer. Their correct use and image interpretation can spare unnecessary biopsies and give the information needed to propose the best treatment option to the patient. The diagnosis of skin cancer is first done by clinical inspection. A good clinical photograph can be useful in understanding the external dimensions of the tumor, the location, and the size in relation to the anatomical area. Dermoscopy is probably the most commonly used and versatile NIIT, and its sensitivity has been vastly proven [6]. It can be used to identify structures which indicate histologic nature of the tumor [7] and has been found to be a useful tool in the preoperative prediction of the BCC subtype as well as the noninvasive assessment of tumor response to topical treatments [8, 9]. However, the evidence of the studies is limited, and in equivocal lesions, the BCC subtype must be assessed histopathologically [10].

Dermoscopy, however, gives bidimensional tumor information (superficial length and width). For depth and shape (volume), ultrasound is the most useful and versatile technique. High-frequency ultrasound equipment can be used

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with probes that can range from 15 to 100 MHz. For skin malignancies, 22 MHz is usually sufficient to view the epidermis, dermis, and part of the subdermal tissue. This probe gives a resolution of around 72 μm and penetrates as deep as 8–10 mm. This is sufficient to visualize volume, shape, and actual size of most keratinocyte carcinomas of the skin. This information is crucial for treatment decision as superficial tumors like in situ squamous cell carcinomas and superficial basal cell carcinomas may be treated with other methods than surgery and still obtain satisfactory oncologic results. Its cost makes it more affordable than optical coherent tomography, which gives similar information regarding depth and volume, but is a more expensive device. HFUS has also the advantage that the learning curve for KC is steep as it is basically based on identifying the tumor, taking the measurements (depth and length), visualizing shape, and recognizing structures such as granules that help identify its histologic nature [11]. The image of the subepidermal structures generated through the technique can help the surgeon decide the excision margin needed or identify admixture tumors (those with more than one histologic subtype).

To reach a correct decision regarding what to do with each type of tumor, an individualized analysis for each case should be performed including the triad: patient-tumor-treatment modality (Fig. 12.1).

The Need for a Variety of Therapeutic Approaches and the Role of HFUS

As the number of patients with skin cancers increases, it becomes more relevant to give patients surgical and nonsurgical options, specially when treating low-risk KC [12]. There are patients that do not wish to have surgery [13]. Shared decision-making is important because it gives the opportunity to explain about the tumor characteristics and the risks associated with each treatment option and then to involve the patient in choosing what is best for him/her.

For low-risk tumors, patients should be aware that surgery is not the unique choice for tumor removal and that it also has its hazards. As most KC occur in the elderly, it is crucial to offer options with low morbidity and risk. Patients with diabetes, coagulopathies, blood-borne infections, mobility problems (wheelchair or bedridden patients), allergy to local anesthesia, and multiple lesions and those with other comorbidities are among the ones that may benefit from selecting alternative options while they may be reassured of acceptable oncologic and cosmetic results.

HFUS gives the possibility to see the shape of the tumor. Most nodular BCCs are round/oval, and margins are easily determined by simple clinical/DMS observation. Some SCC get larger

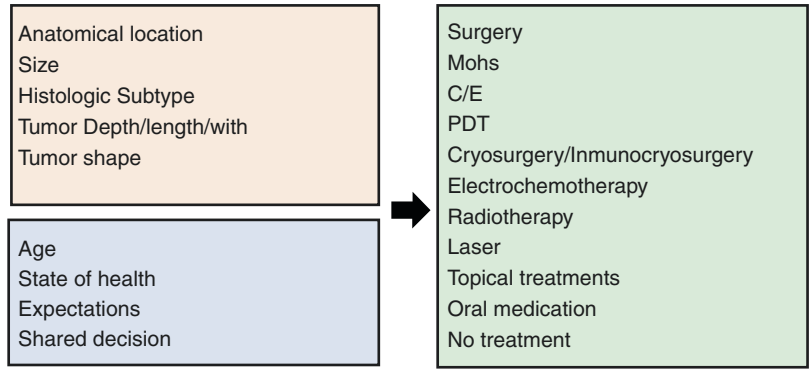

Fig. 12.1 Before taking a therapeutic decision for a malignant tumor of the skin, it is mandatory to have all possible information on the patient (bottom pink left square), on the tumor (top pink left square), and on all the possible treatments (right green square)

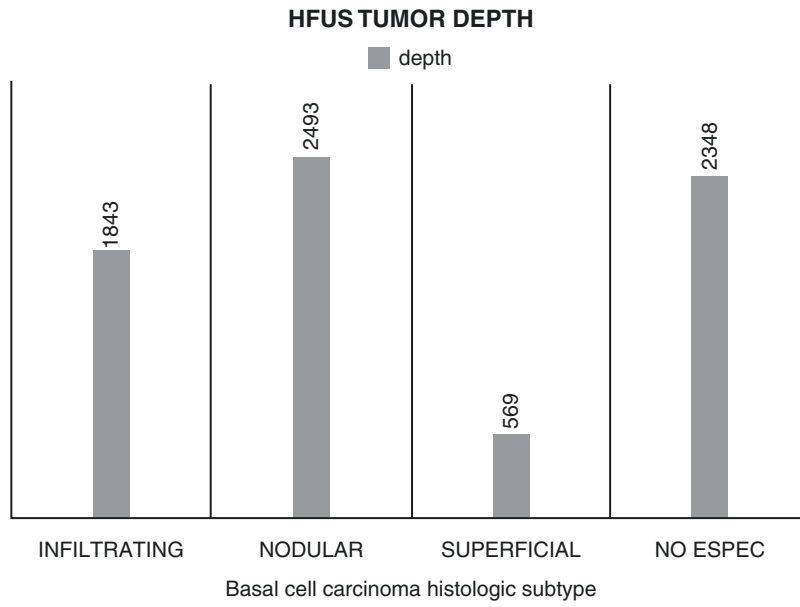

Fig. 12.2 HFUS tumor thickness relates to histologic subtype. Superficial BCCs are of less than 600 μm

as they get deeper (iceberg type). Knowing the shape of the lesion will be of great aid for deciding the best treatment option.

Thickness is related to the histologic subtype. In a study (non-published data), we took HFUS on 72 BCCs. Histologically, 15 were infiltrating, 17 were nodular, 26 were superficial, and 14 had no report on subtype. The mean depths measured by a 22 MHz HFUS for each subtype were 1843 μ (infiltrating), 2393 μ (nodular), 569 μ (superficial) , and 2348 μ (non-reported). In the latter tumors, the pathologist excluded superficial BCC, but the size of the sample did not allow to specify among infiltrating or nodular (Fig. 12.2).

Additionally, HFUS is also important in visualizing admixture tumors. These refer to those BCCs with more than one histologic subtype, such as superficial BCC with areas of nodular BCC.

Cryotherapy as a Treatment Option for Keratinocyte Carcinomas

Cryosurgery stands among the most versatile surgical techniques. It has a steep learning curve; it is of low cost and is easily accessible, and oncologic results are comparable to conventional surgery for low-risk BCC. Wound healing occurs by secondary intention, which makes it ideal for difficult-to-operate areas, like nostrils and earlobes. For skin cancer destruction, there will be a hypopigmented scar in the area treated, which sometimes is accompanied by a hyperpigmented halo. It is important to keep this in mind when treating darker skin types and tumors in visible areas.

For skin cancer, two freeze-thaw cycles are needed. The temperature required at the periphery and depth of the tumor should be below −55 °C in order to efficiently destroy malignant cells [14]. During the first freeze-thaw cycle, tissue destruction mostly occurs in the center of the ice ball, where the temperature is the lowest with destruction mostly due to cell necrosis. Low temperatures applied at a fast-freezing rate will cause vascular injury at the periphery. During the first freezing cycle, there will be intra- and extracellular ice formation and osmotic changes that will cause cell bursting. Cells that survive from the first freeze cycle are partly damaged, and a second freezing cycle will cause ice crystal formation inside them. The concomitant effect will be bursting and cell death. There are other mechanisms that might also be responsible for cell death: apoptosis—which occurs around 8 h

Table 12.1 Cryosurgery generates many types of damage to the tissue that occur at various time periods and affect it in different ways

	Mechanism	Timing	Location
Direct injury	Extra- and intracellular ice crystal formation + coagulation necrosis	Freezing phase	Center of the cryoinjury
Vascular injury	Microcirculatory failure + ischemic necrosis	Thawing phase	Periphery of the cryoinjury
Apoptosis	Cell death by apoptosis	Up to 8 h after rewarming	Periphery of the cryoinjury
Immunological	T-cell response mediated by dendritic cells	Late event	Whole body

This table shows the type of tissue damage (direct/vascular/apoptosis/immunological), mechanism, timing, and location

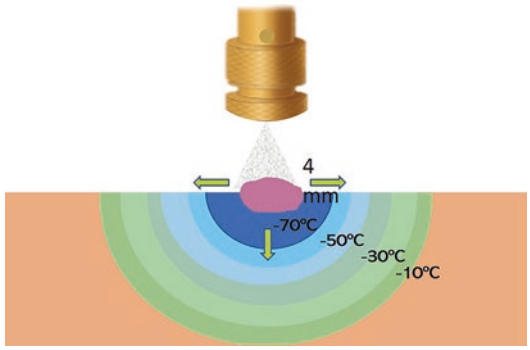

Fig. 12.3 The skin ice ball resembles a half sphere. Cold expands in isotherms, the center being the coldest part and the periphery the warmest. To destroy a cancer cell, it is required to double freeze it at −50 °C. Therefore, the high-risk area for recurrence is in the periphery as suboptimal temperature can allow for cancer cells to survive

post-thawing—and a T-cell immune response mediated by dendritic cells, which is triggered by the residual tumor mass (Table 12.1).

It is known that cancer cells require −50 °C to –60 °C to be destroyed. Measuring the temperature in the treatment field is possible by using thermocouples or, more recently, by infrared thermometer surface measurement. As the freezing front advances in the skin, a half-sphere ice block is formed. Temperature expands in isotherms [15] (Fig. 12.3). Therefore, it can be measured at the border of the 5 mm margin, and this will be the same as the temperature at the depth. It is only through infrared thermometer measurement that the cryosurgeon can know precisely the temperature achieved, and it is with the HFUS that one can confirm the extension of the freezing front.

Trans-Cryosurgical Control with HFUS

Once a tumor is frozen, HFUS can be used to visualize the depth of the freezing front [16]. Immediately after freezing, the image obtained is totally black because the ice block will not allow the echosonographic wave to expand through the tissue. As time passes, thawing begins at the surface of the area treated, while the deeper tissues still stay frozen and therefore remain not visible (black) (Fig. 12.4). It is possible to see the thawing advance with time, as the visible limit of tissue moves deeper. Once complete thawing of the tissue has taken place, edema in the treated area will appear. The tumor will then look more dense and its boundaries less precise (Fig. 12.5a, b).

Cryobiopsy and Ex Vivo HFUS

Cryobiopsy is the name given to the technique used to obtain a shave biopsy of a previously frozen suspicious lesion. The advantage is that cold generates partial “anesthesia” of the area, sufficient for shaving the tissue and not causing pain to the patient. It has the advantage that it does not require local anesthesia. Topical freezing is the anesthetic itself. This is ideal for patients allergic to local anesthetics, needle phobic, and sensitive areas (for instance, nose and genitalia). It reduces time and expenses (no syringes nor anesthetics are needed).

For small tumors, a shave biopsy can be sufficient to remove a tumor. Once the shaving has been performed, the sample can be placed in a gauze and

a HFUS performed on the extracted piece. This visualization will confirm if the tumor has been removed completely [17] (Fig. 12.6a, b).

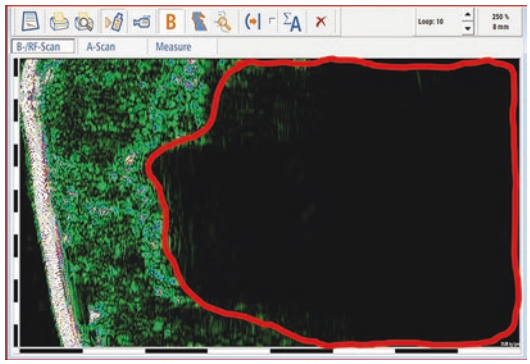

Fig. 12.4 Immediately after freezing and during the thaw period, the ice block can be seen at the deepest part (the black area inside the red line)

Contraindications

Histological control of the damaged tissue is not always possible using cryosurgery, which is essentially a destructive treatment approach. Moreover with this technique, deeper parts of tumors might not be reached because of penetration limits or only with an inappropriate risk of tissue scarring (e.g., deep cryotherapy) [5]. As a rule, blind techniques should be avoided in BCC, in which a deeper tissue invasion cannot be ruled out and in those at increased risk for subclinical spread or local recurrence as well as in invasive SCC where there is a risk of recurrence and metastasis.

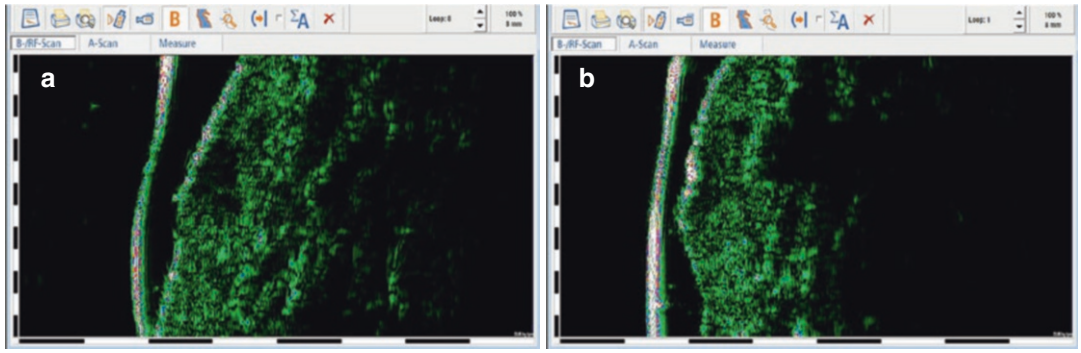

Fig. 12.5 (**a**) (On the left) Shows a small Bcc, which was later treated with cryosurgery. (**b**) (on the right) The same lesion in (a) immediately after cryosurgery showing evidence of post-cryosurgery edema

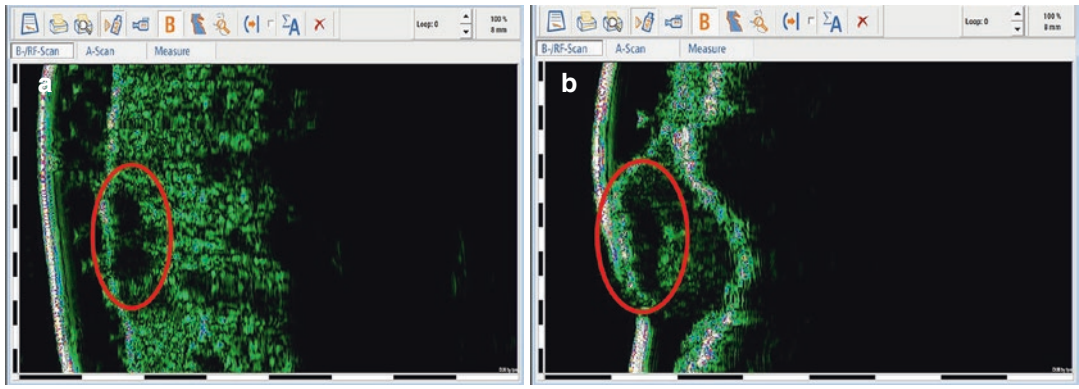

Fig. 12.6 A small BCC (**a**) is frozen and shaved. An ex vivo HFUS of the extracted part (**b**) shows the entire tumor surrounded by healthy tissue

Conclusions

With the continuous increase in KC incidence and the presence of these tumors in the very elderly, there is a clear need for treatments alternative to surgery. Implicating the patient in the therapeutic decision appears to be more and more necessary, as not only the tumor but also the patient's choice should play a role in defining the appropriate treatment after considering all possible approaches. The combined use of cryosurgery with HFUS for low-risk KC offers the benefit of applying a minimally invasive destructive treatment without the complete "blindness" that usually characterizes it, as there is a synchronous visualization of the tumor's shape and volume. Furthermore, for experienced users of this combined approach, more information can be obtained additionally either by trans-cryosurgical control of the ice block depth or by ex vivo examination of the tissue removed. Careful selection of candidate patients for this method is important as it can be an excellent alternative for low-risk cancers in very old patients, but it should be avoided in high-risk tumors for recurrence and metastasis.

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