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Review

Cutaneous Cryosurgery in Dermatology: Evolving Principles and Clinical Applications for Benign, Premalignant, and Malignant Lesions

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Abstract

Skin and subcutaneous diseases represent a significant public health burden, profoundly impacting quality of life, social interactions, mental health, and daily activities–raising concerns worldwide. In modern cryogenics, cryosurgery is among the therapeutic approaches employed by healthcare professionals to address this broad and complex range of diseases. Over the past four decades, cryosurgery has evolved into a valuable treatment option, used alone or as an adjunct therapy, and is adaptable to the needs of various special populations. This approach offers distinct advantages over established treatments due to its safety, efficiency, feasibility, and cost-effectiveness. However, a comprehensive, up-to-date review of cryosurgery's applications is lacking, which limits research dissemination and recognition among dermatologists. This review aims to provide an overview of cryosurgery principles and its current clinical practice in dermatology, covering a broad range of benign, premalignant, and malignant cutaneous conditions, and highlighting its potential as an essential approach in global healthcare.

Keywords: Cryoablation, cryogenics, cryosurgery, cryotherapy, dermatology, liquid nitrogen, skin diseases, skin lesions, treatment, review.

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Introduction

Skin and subcutaneous diseases represent a significant public health burden worldwide, with prevalence rising continuously–most notably by 47% between 1990 and 2017 (1). According to data from the Global Burden of Disease (GBD) study, skin diseases rank as the 18th leading cause of disability-adjusted life years (DALYs) and the 4th leading cause of disability globally. Excluding mortality, the years lived with disability (YLDs) from skin diseases exceed those caused by diabetes mellitus (36.4 million *vs.* 29.5 million). Research consistently highlights the profound impact of these conditions on quality of life, social interactions, mental health, and daily activities (2). A recent study by Kanji (3) on common chronic dermatological conditions–such as eczema, psoriasis, acne, rosacea, vitiligo, seborrhoeic dermatitis, and skin allergy–identified key aspects of daily life affected, with stress levels and mood being the most frequently impacted, as shown in Figure 1. These findings reinforce substantial research linking the onset or worsening of various skin diseases to stress, which severely impacts patients' psychological and physical well-being. Stress is considered a major factor in up to 85% of dermatological patients, influencing both the incidence and progression of skin conditions. This occurs primarily through disruptions in the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), and neuropeptides (4). Additionally, the visible effects and social stigma associated with many dermatological conditions further intensify the psychological burden, creating a cycle of escalating stress and worsening skin disease, as illustrated in Figure 2. Stress-induced changes can also disturb the balance of immune cells and inflammatory mediators in the skin, leading to dysregulation and heightened susceptibility to other skin conditions, including tumors.

Various factors are known to predict psychosocial stress in dermatological patients, including specific demographics, social stigmatization of visible skin conditions, occupational challenges, frequent (often costly) healthcare appointments, and disease-related factors such as symptom number, severity, and duration (5). Consequently, patients with skin

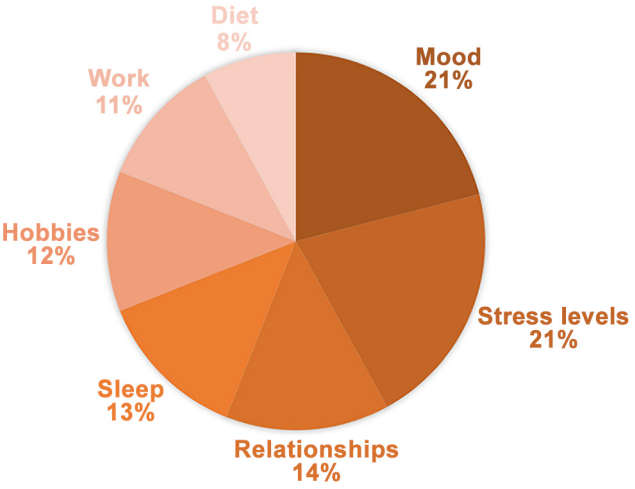

Figure 1. *Aspects of life impacted by chronic skin conditions (3).*

conditions face significant psychological issues, including feelings of anxiety, anger, rejection, shame, depression, social isolation, embarrassment, and low self-esteem. These issues can further impair their ability to socialize and sustain personal and intimate relationships. In a study by the British Skin Foundation (6), 56% of respondents reported difficulties in making friends, low self-confidence, and reduced sexual performance; 29% indicated that their skin condition was a barrier to finding a partner, and 20% attributed it as a major factor in a breakup. Of even greater concern is the evidence linking skin conditions to an increased incidence of clinical depression, clinical anxiety, and suicidal ideation, particularly among patients with acne, eczema, psoriasis, alopecia areata, atopic dermatitis, and hidradenitis suppurativa. The comorbidity of dermatological conditions and mood disorders was investigated in an international multicenter observational study by Dalgard *et al.* (7), using the Hospital Anxiety and Depression Scale. The study reported clinical anxiety in 17.2%, suicidal ideation in 12.7%, and clinical depression in 10.1% of patients, as shown in Figure 3. Despite their high prevalence and strong association with psychiatric disorders, skin diseases are often overlooked and underestimated due to their generally non-life-threatening nature. Additionally, dermatology has been among the most adversely affected specialties by

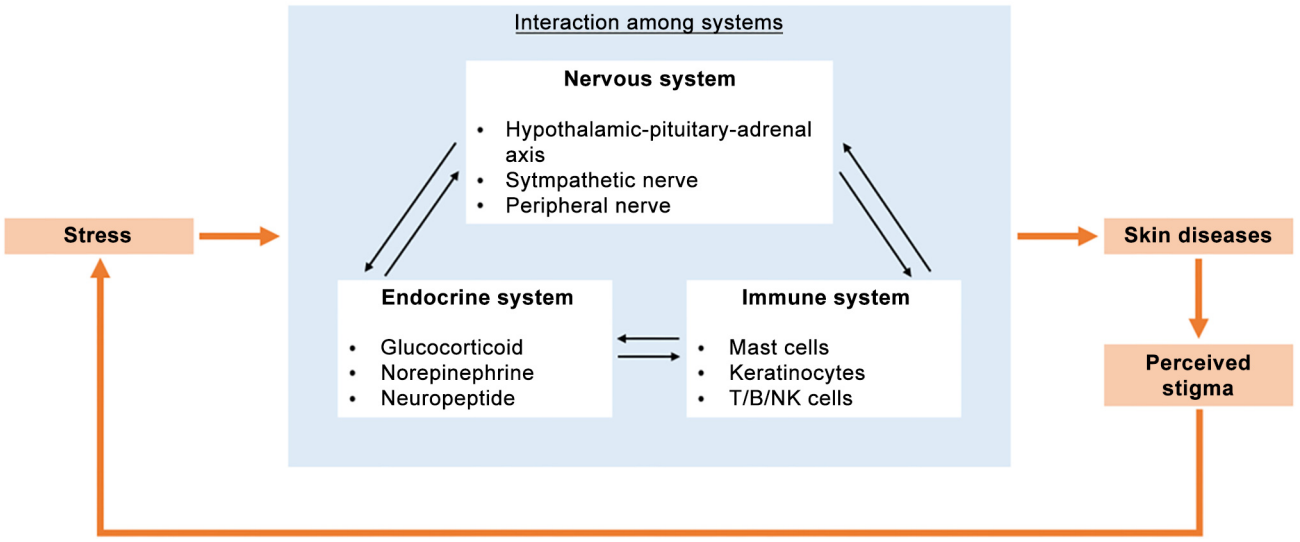

Figure 2. *The vicious cycle between psychological stress and skin diseases (4).*

government reforms, facing challenges such as inadequate resources, a shortage of dermatologists, and long wait times of up to 5 months to 2 years. These factors have hindered progress in providing the necessary medical, psychological, and social support over the past decade. A comprehensive framework of targeted and effective interventions is essential to address, destigmatize, and holistically treat these patients, thereby improving their quality of life and addressing related comorbidities. Local and national support, dermatological research, education, and clinical application are crucial components of this global health effort.

Among recent technological advances, cryosurgery stands out for its combination of efficiency, safety, cost-effectiveness, ease of use, and adaptability to treat multiple lesions in a single session. It offers optional anesthesia, low infection risk, minimal wound care, no suture removal, a short recovery period, no restrictions on work or sports, excellent cosmetic outcomes, and portable equipment. Cryosurgery is highly adaptable to the needs of various populations, including the elderly, children, pregnant and lactating women, individuals with disabilities or mental health challenges, and institutionalized patients. It may also benefit patients with HIV and has palliative applications in

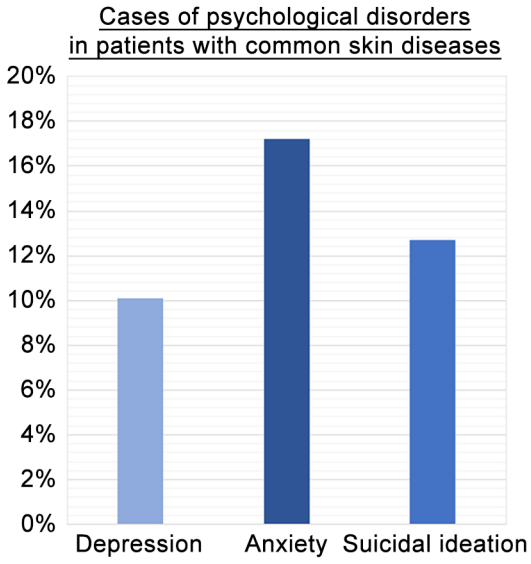

Figure 3. *Co-occurrence of depression, anxiety, and suicidal thoughts in patients with common skin diseases (7).*

melanoma and epithelial tumors, both primary and metastatic. In selected cases, cryosurgery can be enhanced by combining it with other treatments, such as topical chemotherapy, immunotherapy, hyperthermia, sclerosing agents, or systemic therapies. Cryosurgery is effective in

Table I. *Indications of cutaneous cryosurgery (8, 9).*

Benign	
Acne	Lichen planus
Acrochordon (skin tags)	Lichen sclerosus et atrophicus
Adenoma sebaceum (facial angiofibroma)	Lichen simplex chronicus
Angiokeratoma	Lupus (erythematosus, vulgaris)
Angiolymphoid hyperplasia with eosinophilia	Lymphangioma circumscriptum
Angiomas	Lymphocytoma cutis
Callosities, corns, clavi, tylomata	Molluscum contagiosum
Cheilitis and miscellaneous benign lip lesions	Milia en plaque
Chloasma (melasma)	Myxoid cyst
Chromoblastomycosis	
Chondrodermatitis nodular helicis	Post-herpetic neuralgia
Clear cell acanthoma	Nevus sebaceous
Condyloma acuminatum (genital warts)	
Cylindroma	Orf
Dermatofibroma	Pearly penile papules
Dermatosis papulosa nigra	Plantar lesions
	Porokeratosis of mibelli
Eccrine poroma	Porokeratosis (linear)
Eosinophylic granuloma	Disseminated superficial actinic porokeratosis
Elastosis perforans serpiginosa	Psoriasis
Epidermal nevi	Prurigo nodularis
	Pruritus ani
Fibrous papules of the nose	Pyogenic granuloma
	Purulent diseases of the skin and subcutaneous fat
Granuloma annulare	
Granuloma faciale	Rhinophyma
Granuloma fissuratum	Rosacea
Haemangiomas	Cutaneous sarcoidosis
Herpes simplex	Seborrheic keratosis
Hidradenitis suppurativa	Steatocystoma multiplex
Hidradenoma	Syringoma
Histiocytoma	Sebaceous gland hyperplasia
Cutaneous horn	
Hyperhidrosis	Trichoepithelioma
Hyperkeratosis of the nipple and areola	Tuberous sclerosis complex
Hypomelanosis	
	Venous lakes
Idiopathic guttate	
Ingrown nail	Warts (common)
Keloids and hypertrophic scars	Verruca palmaris
	Verruca plana (flat viral warts)
Cutaneous larva migrans	Verruca filiformis (filiform Wart)
Leiomyoma	
Leishmaniasis	Xanthomas
Lentigo and solar lentigines	Xanthelasma palpebrarum

Table I. *Continued*

treating over 50 types of benign lesions, as well as certain premalignant and malignant lesions, achieving high cure rates, as summarized in Table I (8, 9). However, the current literature lacks an up-to-date review of this evolving clinical practice, which limits research dissemination and broader recognition of cryosurgery. This review paper aims to fill

Table I. *Continued*

Premalignant
Actinic keratosis
Bowen's disease
Carcinoma *in situ*
Keratoacanthoma
Lentigo maligna
Neurofibroma
Porokeratosis
Chronic radiodermatitis
Sarcoidosis
Malignant
Basal cell carcinoma
Nevoid basal cell carcinoma (Gorlin syndrome)
Kaposi sarcoma
Cutaneous leiomyosarcoma
Cutaneous lymphoma
Lentigo maligna melanoma
Mastocytoma
Inoperable melanoma metastases
Squamous cell carcinoma

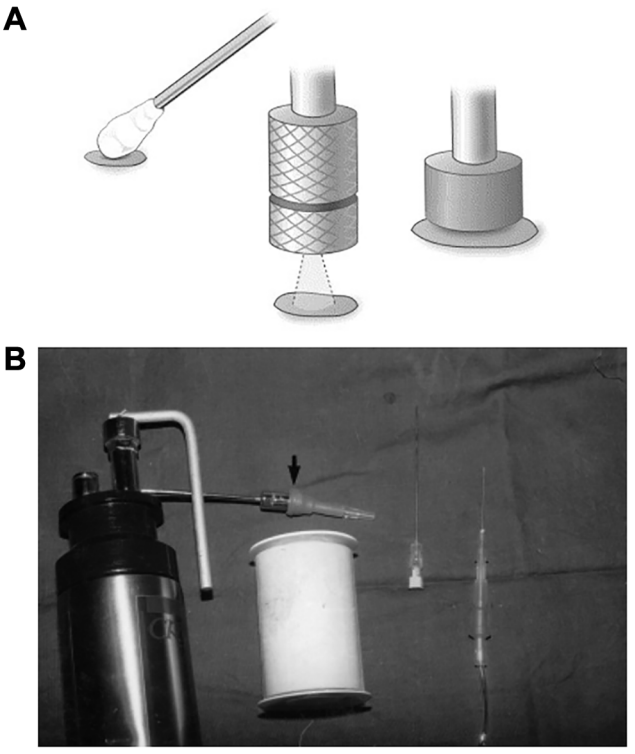

Figure 4. *Cryosurgery techniques in dermatology: (A) contact, spray, and cryoprobe tip (left to right), and (B) intralesional cryoprobe system (10, 11).*

that gap by providing an overview of cryosurgery principles and its current applications in dermatology, highlighting its potential to combat the growing burden of skin diseases.

Modern Cryosurgery Systems

Cryosurgery procedure and technique. The analgesic and anti-inflammatory effects of cold on both body and mind have been recognized since ancient times. With advancements in cryogen liquefaction, industrial production, and the storage of liquid coolants, our understanding of the underlying mechanisms of cryobiology has evolved significantly over the past 200 years. Today, combined with equipment improvements, cold treatment has transitioned from a generalized medical application to a precise, minimally invasive surgical technique–cryosurgery–enabling controlled destruction of tissue, both superficial and internal, through extreme cold (8, 9). This advancement has expanded cryosurgery's clinical applications, making it an invaluable tool across various medical fields, including cardiology, breast, gynecology, pulmonology, urology, gastroenterology and liver, orthopedics, ophthalmology, the orofacial region, and dermatology. Since its first use in dermatology for early-stage epithelioma in 1890, cryosurgery has become a mainstay therapy within the field. It is often performed in outpatient settings, proving superior in feasibility to alternatives such as excision, curettage, electrodesiccation, and superficial radiotherapy. Cryosurgery uses cryogens such as liquid nitrogen, liquid argon, solid carbon dioxide, or nitrogen oxide; liquid nitrogen, with a boiling point of −196˚C, is the preferred modern cryogen. The choice of delivery technique, cryogen type, and dosage depends on the type, size, location, and depth of the lesion, as well as the required depth of freeze. Table II summarizes the techniques of cryosurgery across various benign, premalignant, and malignant dermatological conditions.

Cryosurgery techniques in dermatology can be divided into four main categories that include contact (a

Table II. *Cutaneous cryosurgery indications and general recommendations.*

	Indication	Technique	Freeze time (seconds)	Margin (mm)	Number of freeze-thaw cycles	Number of treatment sessions
Benign	Acne	D/OS/P	5-15	1	1	Once
	Common warts (including anogenital and plantar)	D/OS	10-30	2	1-3	Three times, monthly
	Cutaneous horn	D/OS	10-15	2	1	Once
	Keloid scar	OS/P	30	2	1-3	Three times, bimonthly
	Hypertrophic scar	OS/P	20	2	1	Once
	Skin tags	D/F/OS/P	5	1-2	1	Once
	Seborrheic keratosis	D/OS	10-15	<1	1-3	Once
	Solar lentigo	OS	5	<1	1	Once
	Molluscum contagiosum	D/OS/P	5-10	<1	1	Twice, monthly
	Ingrown toenail	D/OS	20-30	2	1	Twice, bimonthly
	Sebaceous hyperplasia	P	10-15	<1	1	Variable
	Pyogenic granuloma	D/OS	15	<1	1	Once
	Oral mucocele	P	10	<1	1	Once
	Myxoid cyst	D/OS/P	20	<1	1	Once
	Dermatofibroma	OS/P	20-60	2	1	Twice, bimonthly
	Angioma	P	10	<1	1	Once
	Haemangioma	D/OS/P	10	<1	1	Once
Premalignant	Actinic keratoses	D/OS	5-20	1-2	1	Once
	Bowen disease	OS	15-30	3	1-2	Three times, monthly
	Keratoacanthoma	OS	30	5	2	Once
	Lentigo maligna	OS	60	5	2	Once
Malignant	Basal cell carcinoma	OS	60-90	5	1-3	Once
	Kaposi sarcoma	OS	20-40	3	1-2	Three times, monthly
	Squamous cell carcinoma	OS	60-90	5	1-3	Once

D: Dipstick; F: forceps; OS: open spray; P: cryoprobe.

dipstick or a cotton/synthetic-tipped applicator), spray, cryoprobe tip, and intralesional cryoprobe types, shown in Figure 4 (10, 11).

The most widely used and versatile technique in cryosurgery is the spray method, which standardizes the delivery of the desired cryogen dose using a spray gun to ensure optimal destruction of the target lesion with minimal morbidity, as shown in Figure 5 (12). This technique is especially effective for treating superficial, multiple, or irregular lesions, as well as those located on curved body surfaces. Figure 6 demonstrates variations of the technique, apart from direct-spraying, that include the paint brush method of spraying starting from one side and moving up and down across the lesion, the spiral method, and the rotary method (12).

Confining spray using an open cone shield and positioned approximately 1 to 1.5 cm above the lesion can be used when sensitive structures are nearby, while the timed spot-freeze technique with a 5-mm margin is used to treat malignant lesions, shown in Figure 7 and Figure 5C, respectively (10, 12).

Application of liquid nitrogen using a contact technique with a cotton- or synthetic-tipped applicator is sufficient for benign and superficial lesions. The most advanced intralesional technique using cryoprobes and built-in thermometers is mainly used in malignant lesions and

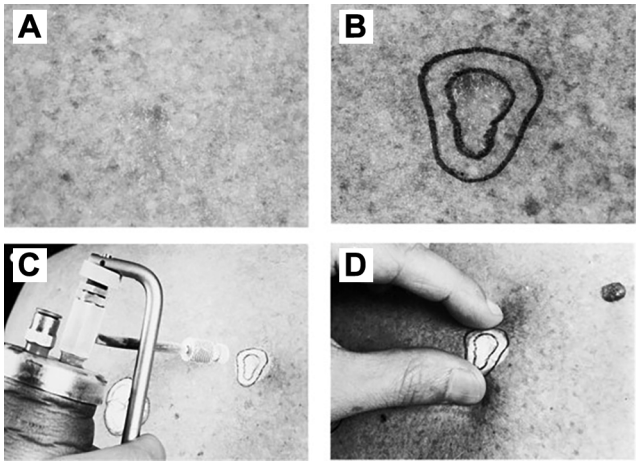

Figure 5. *Cryosurgery of a superficial basal cell carcinoma. (A) The lesion; (B) the lesion and marked margin of surrounding normal skin; (C) freezing procedure using the cryogun; (D) palpating the lesion to ensure adequate ice-ball formation (12).*

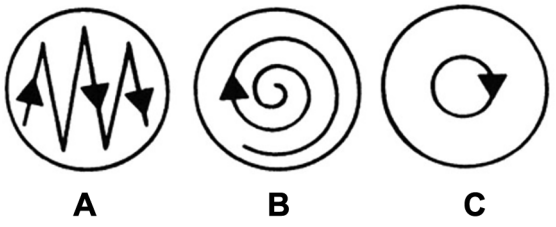

Figure 6. *Spray patterns of cryosurgery spray technique: (A) paintbrush, (B) spiral, (C) rotary (12).*

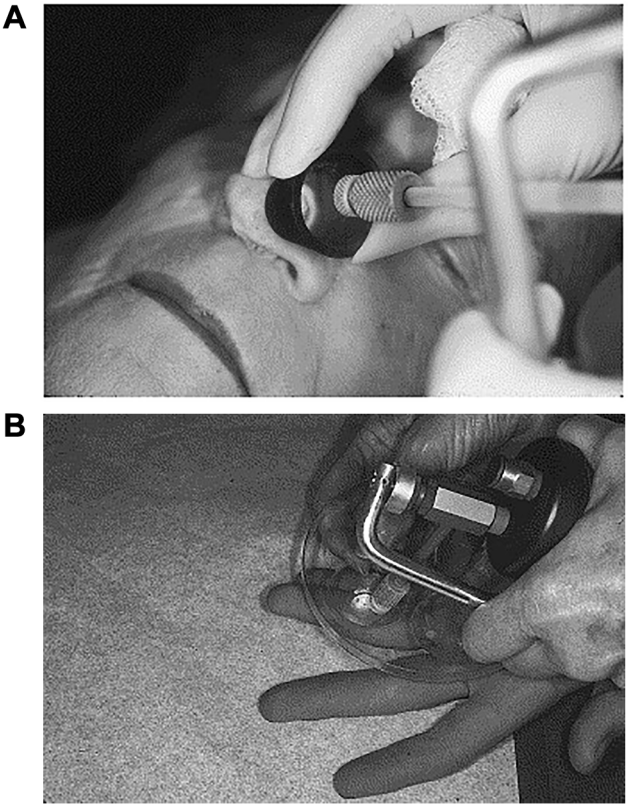

Figure 7. *Confined spray technique (A) on lesion on nose and (B) on lesion on finger (10).*

Figure 8. *Forceps method using liquid nitrogen for freezing benign lesions located in a precarious area such as the eyelid (13).*

keloid scars and is the preferred choice due to epidermis preservation and the absence of hypopigmentation and scarring. In addition, forceps or needle drivers can be cooled by liquid nitrogen and then used to grasp pedunculated lesions, as shown in Figure 8 (13).

Cryosurgery safety in dermatology. Research supports the safety and reliability of cutaneous cryosurgery; however, an interprofessional healthcare team is essential for selecting appropriate candidates following histologic, clinical, or dermatoscopic diagnosis. This team provides counseling on expected outcomes specific to each indication, including tissue damage, healing time, procedural discomfort and pain, dyspigmentation, and eschar formation, as well as potential, though rare, complications. Generally, cryosurgery is well tolerated, with low rates of spontaneously resolving complications such as skin discomfort, pain, erythema, edema,

Table III. *Contraindications and cautions to cutaneous cryosurgery (11).*

Absolute contraindications	Relative contraindications	Perform with caution
High-risk basal or squamous cell carcinoma or melanoma Lesion for which pathology is require Proven sensitivity or reaction to cryosurgery Tumours with indefinite margins Unable to accept possibility of pigment changes	Agammaglobulinemia Cold intolerance Cold urticaria Cryofibrinogenemia (large areas) Cryoglobulinemia (large areas) Immunosuppression Impaired vascular supply Multiple myeloma Pyoderma gangrenosum Raynaud disease (digital cryosurgery most concerning) Unexplained blood dyscrasia	Anticoagulant use Blistering disorders Dark-skinned persons Infants Older persons Sensory loss Sun-damaged or irritated skin Therapy overlying a bony prominence

Table IV. *Cutaneous cryosurgery complications (11).*

Type of complication	Adverse effect
Immediate	Bleeding, blistering, oedema, nitrogen emphysema, pain, vascular headache, vasovagal syndrome
Delayed	Bleeding, excessive granulation, infection, tendon rupture, ulceration
Prolonged but usually temporary	Altered sensation, hyperpigmentation, hypertrophic scarring, milia, pyogenic granuloma
Prolonged but usually permanent	Alopecia, atrophy, cartilage necrosis, hypopigmentation

hemorrhagic blisters, or headaches. Less commonly, patients may experience dyspigmentation, paraesthesia, scarring, or alopecia. Common contraindications, typically linked to concurrent conditions, cautions, and potential complications, are summarized in Table III and Table IV.

Basic Concepts in Cryobiology

Biophysics and biomechanics of cryosurgery. Cryosurgery achieves cooling and destruction of diseased tissues by delivering a cryogen that expands or vaporizes, extracting heat from the surrounding tissue and creating an ice ball. Several heat transfer mechanisms are involved in cryosurgery, including conduction, convection, metabolism, and phase change. Conductive heat transfer is considered the primary mechanism in biological tissues during cryosurgery. In this process, the rate of heat transfer between tissue and blood is proportional to the product of the rate of volumetric perfusion and the temperature difference between local tissue and arterial blood. This relationship is represented by the following equation (1):

$$h_b = V\rho_b c_b(1-K)(T_a - T) \quad (1)$$

where: h_b is the rate of heat transfer per unit volume of tissue; V is the perfusion rate per unit volume of tissue; p_b is the density of blood; c_b is the specific heat of blood; K is a factor that accounts for incomplete thermal equilibrium between blood and tissue; $(0 \leq K \leq 1)$, for some cases $K=0$; T_a is the temperature of arterial blood; T is the local tissue temperature.

Conduction significantly influences the temperature distribution within a lesion. Air is a poor conductor of heat, so as the distance from the applicator tip increases, the minimum temperature rises, cooling rates slow, and thawing rates accelerate. Spray techniques applied from a distance are less effective than techniques where the spray tip is held closer to the lesion or when using contact and cryoprobe applications. Keratin, a protein found in

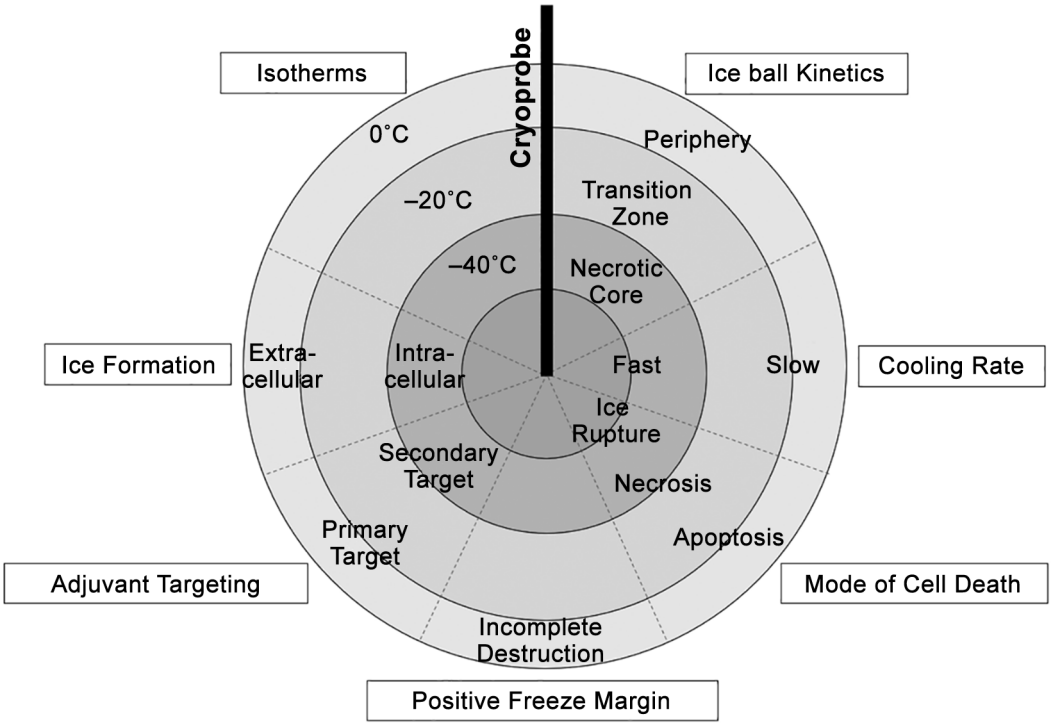

Figure 9. *Schematic representation of the dynamics and events of the freeze zone.*

epithelial cells, also conducts poorly, thus debulking hyperkeratotic lesions before cryosurgery is advisable.

During cryosurgery, the freezing front progresses horizontally and vertically along the skin surface in an isothermal pattern, as shown in Figure 9. The temperature continues to drop until the heat extracted from the tissue equals the heat within the cryogenic fluid, with complete tissue destruction occurring within the −0.5˚C boundary of the ice ball. Each isotherm maintains a uniform radius in all directions, dictating the thermal conditions experienced by the cells in the target tissue, the injury mechanism, and, consequently, the outcome of the procedure. Tissue cells located near the applicator (probe) experience faster freezing rates and lower temperatures compared to cells on the outer edge of the lesion, where temperatures are near body temperature. Benign cells are typically ablated at −20˚C, while more resilient cancerous cells require a target temperature of −40˚C to −50˚C. Melanocytes, which produce melanin, are highly sensitive to thermal changes and are damaged at temperatures below −5˚C. Therefore, the effectiveness of cryosurgery largely depends on the surgeon's ability to anticipate the critical isotherm, which varies according to the specific case and indication.

The basic cryosurgery technique consists of rapidly freezing target tissue to a lethal temperature, followed by a relatively slow thaw, and repeating the freeze-thaw cycle. This approach aims to achieve maximum tissue destruction within the targeted area while minimizing damage to surrounding healthy tissue. The effectiveness of cryosurgery depends on controlling several key parameters: ice front position, cooling rate, temperature, holding time, freeze-thaw cycles, and thawing rate.

Since tissue response varies with the intensity of cryogenic injury, individual evaluation of cooling rates and target temperatures is essential due to variations in tissue thermal profiles and sensitivities. Nonetheless, reaching an end-point temperature below −40˚C is considered a crucial factor for tissue destruction, triggering ice crystal

formation, pH shifts, impairment of homeostasis, membrane disruption, and thermal shock.

Holding time becomes significant if tissue is held at temperatures warmer than −40˚C to intensify the destructive effect but is less relevant below −50˚C. A slow thaw rate within the −20˚C to −25˚C range is particularly advantageous, as it encourages the growth of ice crystals, enhancing tissue damage through microvascular failure and stasis. Repeating freeze-thaw cycles further disrupts cellular thermal stability, causing cumulative intracellular ice formation and increasing cell death. Additionally, it provides structural support for wound healing and optimal cosmetic outcomes. Ideally, repetition should occur between −20˚C and −30˚C. The acute inflammatory response within the first 24 hours further contributes to cell destruction, reinforcing the therapeutic effects of cryosurgery.

Mechanisms of cryoinjury. Cells sustain cryoinjury by multiple mechanisms, broadly categorized into immediate and delayed, specifically into cellular, vascular, and immunological (12, 14-16). During rapid cryogenic freezing, direct cell injury occurs due to both intracellular and extracellular ice formation, as well as a shift in the osmotic balance of the cell. Low temperatures trigger ice nucleation in the extracellular space, leading to biophysical changes within the cell depending on its location relative to the probe. Slow cooling rates and the presence of extracellular ice cause an increase in solute concentration outside the cell, resulting in an osmotic imbalance (ΔΠ) across the cell membrane and cellular dehydration. This process is influenced by the geometry of the specific cell or vascular unit and the membrane permeability (Lp) between the cellular and extracellular compartments. This relationship is expressed in equation 2:

$$dVdt = -L_p A \Delta \Pi \quad (2)$$

where: V is volume of the cell/vascular unit; A is the surface area of the cell/vascular unit; L_p is membrane permeability; $\Delta\Pi$ is osmotic imbalance.

As a consequence of dehydration and the presence of high salt concentrations, it has been suggested that damage to the enzymatic machinery and destabilization of the cell membrane occur. In association, higher cooling rates closer to the probe cause water to get trapped within the cell, supercool, nucleate, and eventually yield intracellular ice formation that is associated with mechanical damage of the cell organelles and membranes. The probability of intracellular ice formation is calculated based on the cellular supercooling (ΔT) and cell parameters as shown in equation 3:

$$PIF = f(V, A, \Delta T, \Omega, \kappa) \quad (3)$$

where: V is volume of the cell/vascular unit; A is the surface area of the cell/vascular unit; Ω is the kinetic parameter of heterogenous nucleation; K is the thermodynamic parameter of heterogenous nucleation.

Post-thaw analysis of injury in cell suspensions has also shown that the melting of ice within the extracellular space, which occurs before the intracellular ice during thawing, leads to a shift of an osmotic fluid of water into damaged cells and therefore, causes swelling and bursting of the cell. Furthermore, biocidal effects are exacerbated by an influx of free water into the intracellular space, which results in the growth of intracellular ice crystals. Indeed, this growth can continue even as melting proceeds in the extracellular space, presumably as a consequence of high extracellular solute concentrations that lower the freezing point of water within them.

Cells that are not affected by direct injury can be subsequently destroyed by morphologic and biochemical changes of apoptosis seen in the periphery of ablation zones and characterized by chromatin condensation, genomic fragmentation, cell shrinkage, and membrane blebbing that are instigated by a signal from intracellular damage to mitochondria and consequent activation of caspases and cleaving of various proteins.

A second mechanism of damage is termed vascular injury that starts during freezing when ice crystals propagate along the vascular system and induce

mechanical damage to the vascular endothelium. Cells surrounding the blood vessels also dehydrate and cause expansion and damage to the blood vessel endothelium and underlying basement membrane, subsequently resulting in a thrombus formation and ischemia that itself hinders repair and cause regional hyperemia due to the production of vasoactive substances. The associated cascade of molecular events increases vascular permeability, thereby producing oedema of the tissue and ensuing an influx of inflammatory neutrophils and macrophages, overall causing additional damage to the remaining endothelium. The process lasts from weeks to months and culminates with a zone of coagulation necrosis that is surrounded by neutrophils in its periphery.

Immunological injury is another mechanism to induce damage after freeze-thaw, but experimental evidence in support of it is sparse. One process proposed is based on the production of antitumor antibodies and the transformation of B cells with antibodies specific for the antigen into plasma cells. As a result, the formed antibody induces complement fixation, chemotaxis of neutrophils and macrophages, and the associated release of free radicals and enzymes. Another way of immune system involvement is the induction of cytotoxic T cells that become sensitized or through a change in presentation of antigen. Finally, low-temperature application can stimulate the activity of natural killer cells.

The loss of microcirculatory support as a consequence of direct endothelial injury, free-radical formation, thrombosis, and inflammation is critical in defining the extent of cryoinjury after freeze-thaw and is associated with the amount of temperature excursion in the target tissue.

Clinical Practice in Dermatology

Numerous exhaustive data-based studies have documented the increasing incidence of skin and subcutaneous diseases, along with the growing clinical and economic burden of their care, raising serious concerns in medical practice about the effectiveness of existing algorithms and protocols for patient management (1-3). This has highlighted the urgent need to establish superior treatment approaches. Cryogenics has attracted particular attention from the dermatological community due to its high potential to address challenges and risks associated with current treatment methods. However, its application to skin lesions was limited by the lack of adequate instruments, and only in recent decades has active development advanced cryosurgical methods for treating skin growths and lesions of various histopathologies, locations, and sizes (17). Despite its proven success and the increasing body of literature supporting cryoablation's potential in treating skin lesions, research data remain scarce, primarily limited to older short-term results from single-case reports. Therefore, this paper selectively covers only clinical conditions with the highest level of evidence in published works.

Benign Cutaneous Lesions

Inflammatory conditions. Onychocryptosis. Onychocryptosis, also known as ingrown toenail, is a common and debilitating nail condition that causes discomfort, pain, and disability if left untreated and is a common source of morbidity throughout the world. Ingrown nails result from the penetration of the nail plate into the subcutaneous cellular tissue and in general go through three clinical stages: the first encompassing inflammation with erythema, oedema, and pain; the second involving bacterial infections and abscess; and the final associated with the formation of exuberant granulation tissue. Management options range from conservative measures reserved for mild to moderate lesions to extensive surgical interventions and complete excision of the plate in severe cases, depending on the stage of the disease. Currently, there is no consensus on the ideal treatment aggravated by the hesitations as to whether the nail matrix needs to be permanently destroyed during the end period of the abscess and granulation stages. Although excision options are considered a gold standard in dermatology, they usually present high recurrence rates, are not cosmetically acceptable, and are associated with an increased risk of infection. Evidently, cryosurgery presents

many advantages in the treatment of mild to moderate-grade ingrown toenails, specifically due to its action in all phases of the pathology, from the functional reversible alterations in the peripheral nerves to reduce pain and the bactericidal property to reduce secondary infection to the ability to destroy the germinative cells of the nail matrix. It is a simple, quick, safe, and cost-effective outpatient procedure that can be carried out without anesthesia and with limited facilities (18). Turan *et al.* (19) retrospectively examined the visual analogue scale (VAS) and dermatological life quality index (DLQI) in onychocryptosis patients treated with cryosurgery. The study evidenced recurrence rates of 34.2% and 88.9% in unilateral and bilateral onychocryptosis, respectively, with 75 to 80% excellent symptomatic responses. Bilateral ingrown toenails, foot or toe deformity, and age younger than 20 years were related to treatment ineffectiveness. In a later observational pilot study in juvenile patients aged 12 to 16 years with unilateral juvenile ingrown toenails, liquid nitrogen spray achieved good efficacy in 91.7% of patients, and adequate symptomatic relief was noted in 83.3% of patients with stage 3 disease, despite the high recurrence rates (45.5%) (20). The effectiveness of topical cryosurgery with liquid nitrogen was evaluated in a recent Sethi *et al.* (21) study, and complete clearance with no recurrence was reported in 74.4% of treated nails, the rest requiring additional intervention of partial or complete nail avulsion. In patients with advanced stages of ingrown nails, matrixectomy using cryosurgery after partial nail extraction has been significantly more successful than matrixectomy using electrocautery (22). Supportive findings have been documented in the Yilmaz and Cenesizoglu (23) study that investigated the effectiveness of cryosurgery following partial nail removal and evidenced treatment success in 97.4% of nails on a 6-month follow-up. Combined treatment option technique has also been reported by Reis and Filho (24), who proposed a new technique of radioelectrosurgery and liquid nitrogen cryosurgery that evidenced efficacy with high rates of cure, ease of application, cost-effectiveness, patient satisfaction, and good cosmetic results. This has been achieved by levelling the lateral nail borders, preserving the morphological characteristics of the nail plate, smooth progression of the healing period, complete removal of granulation tissue and nail fragments, reducing inflammation and pain, little bleeding occurring with a clean surgical field during the removal of granulation tissue, and concomitant coagulation of the small vessels, facilitating the surgeon's work.

Keloid and hypertrophic scars. In the developed world alone, 100 million patients face scar formation, which dramatically affects their quality of life both psychologically and physically, due to associated pain, pruritus, and contractures. Hypertrophic scars and keloids are fibroproliferative disorders that result from aberrant wound healing that occurs in the form of local proliferation of fibroblasts and increased production of collagen. Although a large number of new treatment approaches have recently emerged in an endless stream, the quality of evidence for their efficacy is generally low, with the proportion of therapy resistance and recurrence remaining high, indicating a lack of predictability and consistency in outcomes among the available treatment approaches. The onset of these difficult, deforming, and dispiriting disorders is closely related to the patient's individual constitution; therefore, comprehensive and personalized approaches are the key to achieving optimal outcomes. Into this confusing and frustrating milieu, cryotherapy has emerged as a highly promising and the most advantageous novel approach due to the mechanism of destruction being correlated with the specifics of subsequent reparative processes in tissues. Safety, efficiency, and a low relapse rate can be achieved by the means of monotherapy or in combination in the treatment for hypertrophic scars targeting microcirculatory vessels of the skin and for keloids targeting both the capillaries and the hydrophilic immature connective tissue (25). It is well-evidenced that this direct cell destruction followed by destruction of tissues due to hemodynamic disturbances results in the destruction of microcirculatory vessels and the total necrosis of fibroblasts forming a regenerate, which has a structure similar to that of organotypic regeneration and

the appearance of normal skin. Comparative assessment of intralesional cryosurgery with intralesional injection of triamcinolone and 5-fluorouracil has shown its superiority and ability to accelerate keloid healing with fewer side effects (26). Current methods of cryosurgery have evolved from contact or spray (excellent to good responses in 61.3% of cases) to novel potent intralesional methods that have increased freezing area and usually require only a single treatment, cause minimal damage to the superficial skin, minimal pigmentation changes, and patients experience a shorter recovery period (27, 28).

Har-Shai and colleagues have conducted extensive research that allowed the design of a special liquid nitrogen cryoneedle and confirm the effectiveness of intralesional cryotherapy as a monotherapy for scars. Figure 10 shows the sequential steps of the intralesional cryosurgery procedure and the final result. In their further studies, 51.4% of scar volume reduction was achieved after one session with significant alleviation of objective and subjective clinical symptoms, no adverse effects, and no recurrence (29-31). The histomorphometric analysis has demonstrated rejuvenation of the treated scars, as well as a more organized architecture of the collagen fibers, achieved by creating a normal wound-healing environment. Furthermore, intralesional cryosurgery technique has been found to significantly reduce the dissatisfaction of patients (32). A clear, distinct transition zone that separated the unaffected and the cryo-treated area has been observed with the frozen tissue devoid of mast and proliferating cells while the number of blood vessels remained unaltered. Importantly, intralesional cryosurgery provided a friendly surface thermal history that is crucial for the melanocytes in terms of a better survival environment and therefore fewer hypopigmentation, which is of special importance in black or darker-colored skin patients.

Similar findings have been achieved by the Van Leeuwen *et al.* (33) study that reported the average scar volume decrease ranging from 51% to 63% and alleviated complaints of pain and pruritus. On the other hand, no complete scar eradication has been established; recurrences were seen, as well as persistent hypopigmentation in Fitzpatrick 4-6 skin type patients. Ultimately, it was suggested that cryosurgery be used in conjunction with other treatment approaches to further improve efficacy, aesthetics, and symptoms and decrease recurrence rates. For example, a synergy of cryosurgery and intralesional steroid injections, surgical excision, silicone gel sheets, or platelet rich plasma (PRP) injections resulted in superior outcomes compared to monotherapies (34).

Figure 10. *Intralesional cryosurgery procedure of ear keloid and final result four years following a single cryosession (31).*

Elastosis perforans serpiginosa. Rare primary perforating dermatoses, such as elastosis perforans serpiginosa (EPS), for which mainly supportive and no uniform therapy exists, are also amenable to cryosurgery. EPS's inflammatory hyperkeratotic papules formed as a result of transepithelial elimination of abnormal elastic fibers have been successfully treated with liquid nitrogen cryosurgery in a patient with rare EPS type (35). The most common idiopathic type has been similarly effectively treated with liquid nitrogen spray with good tolerability. The effect is believed to be associated with the resulted separation of epidermis from dermis above the basal lamina, which promotes transepidermal elimination of the abnormal elastic tissue (36).

Lichenoid skin disorders. Lichenoids is an umbrella term for flat-topped and often scaly or solitary pruritic cutaneous lesions characterized by a particular type of inflammation. While lichen planus is both clinically and pathologically lichenoid, some lesions can be lichenoid only clinically. Lichenoids range from common to rare, self-limited to malignancy-associated, autoimmune or non-autoimmune conditions with varying epidemiologic characteristics and locations. As the evidence suggests, cryosurgery may confer benefit for these patients by resulting in improvement of clinical signs and symptoms, such as severe itching, as well as in complete resolution. Patients with lichen sclerosus et atrophicus of the vulva treated by a nitrous oxide cryoprobe demonstrated severe itching relief in 75% of cases in the postoperative period and in 50% for three years (37). Supportive findings were reported by the Kastner and Altmeyer (38) study on women and girls aged between 5 and 15 years that experienced improvement of their clinical signs and symptoms in 100% of cases. A meta-analysis of Zhong *et al*. (39) on lichen simplex chronicus noted that the addition of liquid nitrogen cryosurgery treatment to topical ointments is safe and more clinically effective than monotherapy. Lichen striatus with slight pruritus has been addressed in the Stojanovic *et al.* (40) case report, which allowed to achieve successful results: well-tolerability without any side effects and full condition resolution twelve weeks after therapy.

*Prurigo nodularis***.** Prurigo nodularis (PN), a chronic, benign neurodermatitis characterized by severely itching nodules, is another frequent indication for cryosurgery. Having a significant negative impact on patient quality of life, PN treatment is still a challenge. Evidence for the effectiveness of alternative treatment options as cryosurgery dates back to the 1980s, when application of ultra-low temperatures allowed to achieve smooth macule formation and extended relief of pruritus (41). Cryosurgery can be combined with intralesional steroids plus lidocaine and result in disruption of the itch-scratching circle of PN in cases when prurigo nodularis is resistant to standard therapy options. Recently, Mayala *et al.* (42) compared the efficacy of cryotherapy and 0.05% clobetasol propionate and revealed nodule clearance in 100% of patients treated by cryosurgery compared to 27% in the clobetasol propionate arm. Furthermore, cryosurgery was more preferred by patients (63.6%).

Hidradenitis suppurativa. Cryosurgery is a promising treatment option in hidradenitis suppurativa (HS), which is a chronic and recurrent inflammatory skin disorder with a great impact on a patient's quality of life due to the associated formation of inflamed nodules, deep abscesses, draining sinuses, and scars, also accompanied by pain and malodorous and putrid discharge. Although multiple treatment options are available, no optimal protocol can achieve satisfactory remission or cure. Current research appears to validate that cryosurgery using liquid nitrogen can effectively treat persistent nodules of HS not responding to medical therapy with good patient's compliance. Evidence from a Dell'Antonia *et al.* (43) study on liquid nitrogen cryogun demonstrated minimal discomfort and efficiency in 88.7% of patients with persistent nodules of HS. Cryoinsufflation (CI), as a modified spray cryosurgery performed by injecting liquid nitrogen through an ordinary needle, is a novel, well-tolerated, easily conducted, and inexpensive option to minimize both discomfort and the poor appearance of HS lesions. Importantly, it can be effectively combined with other modalities to increase the chance of achieving rapid relief in symptoms and delaying recurrence. Pagliarello *et al.* (44) addressed the most difficult patient populations: patient with HS, Hurley stage III, and myelodysplastic syndrome, and patient who was planning to become pregnant with HS, Hurley stage II, both with unsuccessful previous therapy histories. In both cases, complete symptom control has been achieved without the use of systemic drugs with no recurrence or side effects.

Psoriasis. Another notable potential target for cryosurgery is a lifelong immune-mediated inflammatory systemic and chronic skin disease–psoriasis–which represents a wide

clinical spectrum ranging from scaly erythematous plaques to moderate-to-severe forms associated with a long list of comorbidities. While global epidemiological studies undoubtedly agree on the significant socioeconomic burden the condition has, no effective cure has been established yet, while currently available treatment regimens carry substantial toxicity and usually low efficiency, especially for mild forms of psoriasis. Notably, according to evidence accumulated over four decades, cryosurgery is an effective, simple, and safe therapeutic option in treating and prolonging the remission in localized chronic plaque psoriasis, which is not attainable by other treatment approaches. Importantly, pregnant or lactating females, immunocompromised and elderly patients with comorbidities are amenable to cryosurgery. Clinical findings suggest that application of ultra-low temperatures can improve the induration, erythema, and scaling of psoriatic plaques, especially small ones, by means of physical destruction of lesions and shortening of elongated dermal papillae, resulting in normal reepithelialization (45). Liquid nitrogen cryosurgery performed with a spray or cotton applicator has resulted in a response rate of 67-80% in a first reported study on psoriasis by Scoggins (46). Later studies reported a response-no-response ratio of 6:1 and complete resolution, substantial, or mild to moderate resolution in 88.9% of treated patients (47). In the most recent study by Kumar *et al.* (48) in chronic plaque psoriasis, nitrous oxide cryosurgery allowed to achieve efficient clearance and prevention of relapse in localized plaques with no significant complications.

Acne. The literature contains an array of reports on the therapeutic effect of cryosurgery in one of the most common skin dermatoses – acne – with its characteristic clinical manifestations in the form of non-inflammatory and inflammatory elements. The complex nature of the pathogenesis of this polymorphic disease is dictated by several important factors that include hyperplasia, hyperfunction, and inflammation of sebaceous glands, microbial colonization, and follicular hyperkeratosis, which creates a treatment challenge. While first-line approaches are associated with serious complications, namely microflora resistance after antibiotics and teratogenicity after retinoids, the large number of dedicated studies reveal cryosurgery as a promising alternative approach in the treatment of acne. Published findings to date unequivocally confirm its therapeutic effect based on mechanisms that include restoration of microflora of the facial skin and its appendages, improvement of microcirculation in the foci of dermatosis, normalization of follicular hyperkeratosis, improvement of sebum evacuation, and immunomodulation (12). Furthermore, cryoexposure destructs differentiated keratinocytes, intensifies desquamation of corneocytes in the epidermis, and facilitates exfoliation of the epidermis itself, overall resulting in smoothing the skin micro-relief. To date, dermatologists use liquid nitrogen cryosurgery as a safe, easy-to-use, cost-effective, and efficient approach to treat various types of acne, especially papulopustular, superficial cystic, nodulocystic, or keloidal subtypes; although cryosurgery is not always very effective for treating comedones, nodules, or deep-draining cysts (49).

Viral and Parasitic Infections

Verruca vulgaris and Verruca plantaris. Cutaneous human papillomavirus (HPV) infection of keratinocytes commonly manifests as warts, including common warts (Verruca vulgaris), plantar warts (Verruca plantaris), flat warts (Verruca plana), and anogenital warts (*Condyloma acuminatum*). Although most cutaneous warts are proliferative lesions of benign nature, malignant transformation into cutaneous cancers such as squamous cell carcinoma is documented with high-risk HPV subtypes, including types 6, 11, 16, 18, 31, and 35, and in patients with genital warts and immunocompromised patients. Oncogenic potential leading to epidermodysplasia verruciformis has also been found in HPV types 5, 8, 20, and 47. Albeit consensus and few guidelines for cutaneous warts, comprehensive and systematic guidance for management is missing. Although a variety of therapies have been studied and used for the treatment of warts, none have been shown

to be highly effective in all patients, in addition to being either painful, expensive, or labor-intensive.

Despite limited evidence, liquid nitrogen cryosurgery has been endorsed at dermatology meetings as an effective, safe, established, and simple approach, with a cure rate ranging from 39% to 78% depending on variables in treatment protocol, wart type, and patient characteristics (50-52). Destruction of all pathological tissues along with preserving excellent cosmesis is attained by ablastics of cryodestruction that block the pathological focus and prevent the spread of newly formed viruses. Combined application of the cryogenic agent and daily application of 70% salicylic acid can increase destruction of the verruca with an 89.2% rate of eradication in 86.2% of patients while being a relatively gentle and non-invasive approach (53). Preliminary superior cure rate (70.7%) and safety have been reported after application of a novel combination of nitrous oxide, the specific activation method, and skin-conforming polyurethane foam (54). Nevertheless, more high-quality pieces of evidence with more samples are required to confirm the safety and cost-efficiency of cryosurgery for further recommendations in verruca vulgaris and verruca plantaris owing to a number of comparative studies that critically question the superiority of cryosurgery over other treatment approaches with similar or better efficiency, such as salicylic acid, radiofrequency, duct tape, antivirals, or chemotherapy applications (55-61).

Condylomata acuminatum. In the matter of condylomata acuminatum, which is an anogenital type of warts characterized by multiple and multifocal spread with debilitating symptoms, including itching, pain, increased secretions, and bleeding. The current existence of multiple treatment approaches reflects the fact that none are directly antiviral and uniformly effective. Destruction by thermal-induced cytolysis by cryosurgery is an acceptable, safe, and simple first-line therapy for patients with small to moderate numbers of warts (62). Several studies have reported a 60-90% rate of genital wart clearance, healing in 94% of cases, and a 10-40% recurrence rate by cryosurgery alone or combined with other treatments (63). Response to the treatment in anogenital condyloma acuminata warts has better prognosis in lesions in the vaginal area, the smaller size of lesions, younger age, and shorter duration of infection (64). Significantly improved efficacy has been observed when combined with podophyllin shortening the treatment regimen (65). Supportive findings have been reported by Amar (66) combination of CO_2 laser and cryosurgery. Additionally, low-level quality evidence is available to support the claim that cryosurgery is either superior or inferior to other treatment approaches (67).

It is important to highlight that cryosurgery can be safely and successfully employed on pregnant women on an outpatient basis irrespective of the gestational period, given that a maternal history of condyloma acuminata in pregnancy is a strong risk factor for the development of juvenile-onset recurrent respiratory papillomatosis (68, 69). No fetal, maternal, or neonatal complications and considerably low rate recurrences have been observed, while successful treatment eliminated the need for elective caesarean sections (70, 71). Furthermore, cryosurgery combined with proanthocyanidins can serve as another treatment option for this special risk group of patients (72). Pediatric patients are another amendable group of special-risk patients that demonstrated a favorable response to liquid nitrogen cryosurgery, including the case with unusual anogenital warts (73, 74).

Molluscum contagiosum. Cryosurgery is a practical and cost-effective solution to another viral skin disease–molluscum contagiosum–caused by a member of the Poxviridae family, the molluscum contagiosum virus (MCV). Clinically, the disease manifests as multiple pearl-whitish shiny papules with the umbilicated center, but solitary lesions could also be observed. Owing to high incidence among pediatric patients and increased prevalence in immunosuppressed individuals, these challenging populations are of a particular focus given their association with more numerous and longer-lasting lesions. According to clinical trials, clearance rates from

71% up to 100% could be achieved by liquid nitrogen or nitrous oxide cryosurgery. A hospital-based cohort study by Chapa *et al*. (75) on patients with atopic dermatitis or history of using immunosuppressive drugs demonstrated the clearance rate to be 94%. Al-Mutairi *et al.* (76) compared the efficacy, safety, and acceptability of 5% imiquimod (IMQ) cream with liquid nitrogen cryosurgery for the treatment of molluscum contagiosum in children. While no statistically significant difference was found between the overall complete cure rate at the end of the maximum treatment period, cryosurgery appeared to be the preferred treatment for large solitary or with a smaller number of lesions, with the advantage of being rapidly effective and less expensive than IMQ. On the other hand, IMQ is more preferable for numerous small lesions and appears to be practically painless and more cosmetically accepted compared with cryosurgery. In another comparative study by Muzaffar and Ali (77) on pediatric patients, the cryosurgery group showed complete clearance of lesions in 100% of patients compared to 94.1% in the 10% potassium hydroxide (KOH) solution group, which is a patient-friendlier and relatively safer therapy. Nitrous oxide cryosurgery combined lidocaine/prilocaine topical anesthesia has been evaluated in a Bardenstein and Elmets (78) study on patients with the acquired immune deficiency syndrome (AIDS) with multiple lesions of molluscum contagiosum on the eyelids. Successful regression of lesions has been observed with no complications, demonstrating the approach to be particularly useful and effective in these difficult patients with multiple lesions of the periorbital region. Finally, it is important to note that apart from the promising role of cryosurgery in the treatment of molluscum contagiosum, the approach has been found to improve diagnostic efficacy in solitary lesions that represent a clinical challenge, especially in cases with confusing dermoscopic findings or in doubtful monolesional non-umbilicated cases (79).

Leishmaniasis. Leishmaniasis, a chronic parasitic skin disease caused by protozoal infection, is a growing health concern with a broad spectrum of clinical manifestations and epidemiological diversity with different degrees of severity. With 1.5 million cases worldwide, cutaneous leishmaniasis presents clinically as persistent skin lesions, followed by the formation of a thick scar, and is often associated with secondary bacterial and fungal contamination causing serious complications, including septicemia, tetanus, and even death. There are no vaccines or preventive measures available, and current treatment guidelines are limited due to the variability in disease presentation and poor generalizability. On top of that, the situation is aggravated by the fact that first-line pentavalent antimonials have a high price tag, a variety of systemic toxicities, a significant risk of developing drug resistance, and are unavailable to most patients, especially in impoverished areas where leishmaniasis is most prevalent. To work around these limitations, researchers have observed promising results using local therapy techniques such as cryosurgery. Given the sensitivity of all *Leishmania* parasites to freezing, except for *L. (Viannia) braziliensis*, liquid nitrogen or CO_2 cryosurgery alone or as an adjuvant therapy is a valuable alternative treatment to cure cutaneous leishmaniasis, especially small lesions, with excellent efficiency and cosmesis outcomes and low recurrence rates (80-84). Importantly, adequate cryotreatment of cutaneous leishmaniasis can preclude the development of mucocutaneous extension and therefore further serious systemic complications. According to studies, cryosurgery-treated lesions can exhibit a healing rate as high as >95%, but lower efficacy is also reported (27%). A meta-analysis by Lopez-Carvajal *et al.* (85) provided evidence in favor of cryosurgery given that its efficacy is similar to that of pentavalent antimonials, with additional advantages including a shorter duration and better treatment adherence. Liquid nitrogen cryosurgery has shown superior results to intralesional meglumine antimonate (93% *vs.* 69.7%) and sodium stibogluconate (93.3% *vs*. 89.5%) in terms of cure rates (86, 87). Further evidence borne out by research showed that the synergy of cryosurgery and chemotherapeutic drugs can achieve even better outcomes, resulting in 80-100% healing of lesions (Orabi 2023). These findings are congruent with a

recent publication by Ullah *et al.* (88) on combinational therapy of liquid nitrogen cryosurgery and meglumine antimoniate (MA) as intralesional antimonial that demonstrated more pronounced high effectiveness, owing to lower costs, higher follow-up rate, and shorter treatment duration. Similarly, complete healing was observed in 81.5% of cases in the group that received biweekly liquid nitrogen cryosurgery plus weekly intralesional antimonial, compared to 50% achieved by cryosurgery alone (89). Interestingly, herbal remedies in the form of extracts of fruits and leaves of *Juniperus excelsa (J. excelsa)* can be applied topically as an adjuvant to liquid nitrogen cryosurgery for accelerating the time to cure and increasing the complete cure rate (82% *vs*. 34%) (90).

Chromoblastomycosis. Chromomycosis is skin and subcutaneous tissue mycosis caused by the dematiaceous fungi *Fonsecaea pedrosoi*, *Phialophora verrucosa*, *Cladosporium carrionii*, *Fonsecaea compacta*, and *Rhinocladiella aquaspersa*. The infection results in noduloverrucous lesions in the arms and legs, and one of the most characteristic features is its unresponsiveness to treatment due to differences in antifungal sensitivity patterns and responses among the species, the refractory nature of the disease, and complications as secondary bacterial infection or the development of squamous carcinoma. Surgery is the first choice in the early stages of disease, while systemic antifungals such as itraconazole and terbinafine are necessary in more advanced cases.

Recent clinical experience suggests that cryosurgery with liquid nitrogen is an efficacious option for localized lesions comparable to that of most currently available approaches, with advantages such as the long-lasting cure and cost-efficiency (91, 92). It is also believed that immunologic mechanisms and necrosis are involved in the cure process. Recent publications confirm the efficacious synergistic effect of associating pharmacological oral antifungal treatments with cryosurgery to obtain better results, especially in patients with large, generalized lesions or chronic conditions, reducing the duration of therapy. Evidently, two cycles of liquid nitrogen in an open spray and itraconazole at a dose of 100 mg/day in the case of an elderly patient with chromoblastomycosis in a localized form with a long evolution, resistant to previous drug therapies, resulted in complete regression of the lesions with no recurrence. Importantly, the adopted non-aggressive therapeutic approach allowed the use of a reduced dose of the drug, reducing costs and potential adverse events while providing high clinical cures, crucial for high-risk and chronic patients not amenable to surgical treatment (93). Supportive findings have been reported in a single-case study by Dharmawan and Fiqri (94), who achieved clinical improvement and good results with a combination of itraconazole 400 mg/day for a week for three months (pulse dose) and serial cryosurgery procedures once per week. Liquid nitrogen cryosurgery given every fortnight using large cotton swabs or the cryogun combined with itraconazole pulses (400 mg/day for 7 days per month, 1 week on and 3 weeks off) has been shown as an efficient and cost-effective option shortening the duration of therapy compared with the monotherapies (95). In another single-case study by Bassas-Vila *et al*. (96), two cycles of cryotherapy combined with oral terbinafine for six months allowed to achieve complete cure with no recurrences and only minimal local adverse effects.

Conditions Associated With Sun Exposure

Solar lentigines. Solar lentigines are benign melanocytic proliferations characterized as yellow or brown, oval or round macules with obvious margins. Ultraviolet (UV) radiation is a known carcinogen that contributes to the development of cutaneous cancers. While the strong association has been supported by a myriad of animal studies, *in vitro* studies on human cells, and epidemiological studies, the recent discovery of the common relation between solar lentigines and ultraviolet radiation and between lentigines and cutaneous cancers has provided a valuable insight and unique opportunity to investigate and address the detrimental association between ultraviolet radiation and cutaneous cancers. Many therapeutic

modalities targeting melanin for selective destruction have been advocated in this regard, but even excellent clinical success rates with physical therapies should usually be balanced against associated side effects and recurrence rates. The consensus view seems to validate cryosurgery used alone or in combination with ablative therapy as first-line therapy for these lesions. In a randomized, controlled, prospective trial, Almond-Roesler and Zouboulis (97) compared single treatments of 5 s and 10 s with a contact cryosurgical unit achieving a skin surface temperature of −32˚C. Clinically, both regimens have shown to produce substantial lightening of the lesions in 80% and 100% of patients, respectively, with minimal skin atrophy. Another study on the use of nitrous oxide cryosurgery in solitary large solar lentigo lesions achieved full remission of 100% of the lesions with excellent cosmetic results within a 10-month follow-up period. Therefore, the outcomes confirm the hypothesis of melanocyte vulnerability to low temperatures and corroborate cryosurgery as a successful therapeutic approach for solar lentigo, especially on light-colored skin. In a comparative study by Raziee *et al.* (98), the cryosurgery approach using liquid nitrogen with cotton-tipped applicators was associated with better results than trichloroacetic acid (TCA) 33% solution in the treatment of solar lentigines, particularly in fairer Fitzpatrick skin types, but was more painful and took more time to heal. In another study, liquid nitrogen cryosurgery was similarly superior to argon and CO_2 lasers. Comparable outcomes between cryosurgery and TCA 40% were demonstrated by Goldust *et al.* (99), but again, cryosurgery was associated with higher pain levels and a longer healing period. Accordingly, further validation studies are necessary to validate its efficiency due to contradictory findings from comparative studies that involve frequency-doubled Q-switched Nd:YAG lasers that can provide significantly better lightening and have fewer adverse effects (100, 101).

*Idiopathic guttate hypomelanosis***.** Ultraviolet radiation induction by means of sunlight is also incriminated in the pathogenesis of idiopathic guttate hypomelanosis (IGH), as lesions are mainly located on sun-exposed areas, especially on pretibial areas and the extensor surface of forearms. This common, acquired leukoderma is characterized by multiple, discrete round or oval, hypopigmented to depigmented porcelain-white macules. Although a variety of therapies with variable success have been described, the treatment remains a therapeutic challenge for dermatologists. Cryosurgery with liquid nitrogen has been widely used to treat IGH cases with a small number of lesions, providing repigmentation as well as non-invasiveness, practicality, quickness, safety, and efficiency (102). Positive findings date back to 1990, when Ploysangam *et al*. (103) reported repigmentation in 90% of treated with liquid nitrogen lesions that contained significantly greater numbers of dopa-positive melanocytes in the repigmented areas than in untreated lesions. Supportive outcomes have been achieved by Laosakul and Juntongjin (104) using a cotton-tipped applicator of liquid nitrogen. Assessment at the 4-month follow-up revealed that 82.3% of the treated lesions, compared to only 2% of the control, demonstrated more than 75% improvement with minimal adverse effects. A comparative study between a liquid nitrogen spray gun and 88% phenol has shown cryosurgery superiority in terms of efficiency and safety in inducing pigmentation of IGH macules, as well as in frequency in side effects (105). Specifically, 60% and 16% of cryogenically treated macules showed excellent and good responses, respectively.

Benign Growths

Hemangioma. Owing to the high prevalence rates of cutaneous hemangiomas among newborns and infants and the tendency toward aggressive growth associated with complications such as bleedings, ulcerations, and superinfections, novel approaches that can reflect the needs of this population are of special importance. Cryosurgery has arisen as an excellent treatment and valid alternative to more expensive and complex approaches in such vascular neoplasms with endothelial hyperplasia (74). The Reischle and Schuller-Petrovic (106) study demonstrated that

cryosurgery used early in the treatment of capillary hemangiomas in young patients can yield an excellent to good response in terms of complete remission without leaving scarring or hypopigmentation. Total regression of hemangiomas and regeneration of normal mucosa with no scarring have been noted by Jarzab (107) in cases of hemangiomas involving the face, lips, tongue, and oral cavity. There is additional evidence from the Michel *et al.* (108) comparative study on infant hemangiomas, which demonstrated that cryosurgery is superior to flash lamp-pumped pulsed dye laser (FPDL) in sufficient regression or marked growth inhibition (>50%) of lesions with marked elevated and/or subcutaneous parts (75% *vs*. 68%). Similarly efficient predominant or complete regression (>75%) can be achieved with cryosurgery in initial macular, flat-topped, superficial hemangiomas (68%). Supportive findings have been reported in the Eltayeb *et al*. (109) study on cutaneous hemangiomas in infants and children, where liquid nitrogen cryosurgery achieved complete involution of the lesions in 65% and good results in 25% of cases with no recurrence observed during the follow-up period. Hypopigmentation at the site of the treated area was evident in eight cases.

Clear cell acanthoma. Cryosurgery is a preferred approach in the treatment of benign epidermal tumours as clear cell acanthoma, especially in unusual cases with multiple lesions not amenable to surgical treatment (110). This rare tumor of unknown etiology clinically appears as a slowly growing, well-demarcated, pink to brown, dome-shaped papule or papule-nodule and a peripheral scaling collarette covered with a thin crust and often exuding a slight moisture. Recent evidence borne out by multiple single-case reports supports cryosurgery superiority in treatment of different forms of clear cell acanthoma, including multiple eruptive or elderly patients, as reported by Guarda *et al*. (111) study on a 70-year-old patient with bilateral multiple erythematous papules on legs and thighs that had progressively appeared throughout 30 years. Supportive findings were shown by Monari *et al*. (112) in an unusual case of a 74-year-old patient with multiple clear cell acanthoma on the lower extremities. Cryosurgery with liquid nitrogen and a cotton wool swab resulted in complete resolution of lesions with minimal residual scarring and no relapse at six months follow-up. A rare case of multiple facial clear cell acanthoma has been addressed with liquid nitrogen cryosurgery in a Hatakeyama *et al.* (113) study that achieved almost complete resolution with an acceptable aesthetic result and no sign of recurrence at three months follow-up.

Xanthoma. Xanthoma is an umbrella term for highly prevalent disorders of lipid deposition clinically presenting as cutaneous yellowish-tan plaques, papules, or nodules on of the eyelid and periorbital skin that comprises types as xanthelasma palpebrarum, plane xanthoma, xanthoma tuberosum, tendon xanthoma, and eruptive xanthoma. These deposits are progressive and permanent and can cause significant cosmetic and functional disfigurement. While current treatment approaches possess risks, liquid nitrogen cryosurgery has shown to be a potentially effective and much simpler option. Recently, xanthelasma palpebrarum and tuberous xanthoma have been successfully treated with cryosurgery, with superior cosmetic outcomes and low recurrence rates (114). Labandeira *et al*. (115) reported four cases of successful treatment of xanthelasma palpebrarum with gentle liquid nitrogen spray cryosurgery that achieved complete involution without unsightly perilesional swelling. In the Dewan *et al.* (116) study, nitrous oxide cryosurgery efficiently treated 68% of xanthelasma palpebrarum cases, 6% resulted in slight hypopigmentation, and in 26% recurrence was observed in the form of yellowish papules at the end of a 6-month follow-up. Although a complete response was seen only in 17.5% of the group receiving liquid nitrogen cryosurgery compared to 75% of those receiving 100% trichloroacetic acid (TCA), scarring has been seen only in the TCA group, and the frequency of side effects and pigmentary changes was greater using TCA approach (117).

Digital mucous cysts. Another example of effective application of ultra-low temperatures in benign cutaneous lesions are digital mucous cysts, typically located at the

distal interphalangeal joints or in the proximal nail fold. Although often asymptomatic, these ganglion cysts are associated with pain, tenderness, decreased range of motion, nail deformities, periodic spontaneous discharge, and high recurrence rates; therefore, management involvement is usually required. While there is still no agreement on the treatment of digital mucous cysts due to associated low success rates, greatest risk of recurrence, and problematic healing, multiple reports have described liquid nitrogen cryosurgery as an effective treatment approach following puncturing of the cyst. Successful eradication in 85.7% of treated cases with a two- to five-year follow-up has been reported (118). Importantly, cosmetic outcomes were excellent without evidence of scarring, and there was no recurrence or significant post-cryosurgical morbidity. The cure rate of 86.7% of the total number of lesions and 92.3% for lesions involving the proximal nail fold has been reported by Minami *et al.* (119). No recurrences were noted, and the nail deformity disappeared in 9 months. Bardach (120) have revealed supportive findings on cryosurgery with liquid nitrogen using an intermittent spray technique with no use of local anesthesia. 12 out of 14 patients with prior unsuccessful attempts with other treatment modalities were cured with a high level of tolerability and excellent cosmetic results. Evidence from the Bohler-Sommeregger and Kutschera-Hienert (121) study on digital mucoid cysts and myxoid cysts of the oral mucosa has also shown that liquid nitrogen cryospraying is a valuable therapeutic modality in these notoriously recalcitrant lesions.

Premalignant Cutaneous Lesions

The term 'premalignant' or 'precancer' denotes the lesion containing abnormal cells with an increased risk for malignant transformation. An ever-increasing body of research substantiates the robust evidence on the special precancer significance given the effectiveness of early identification, intervention, and therefore elimination of cancer precursors, potentially leading to the near-eradication of malignancies. Accordingly, such advantages of cryosurgery as minimal invasiveness, efficiency, affordability, ablastics, organotypic regeneration, and the ability to trigger the immune-stimulating antitumor effect while preserving the nativity of pathological structures of the rejected tumor's nucleic acids and proteins are particularly important. As the field continues to expand and evolve, the state-of-the-art cryosurgical methods can ensure radical therapeutic effect for various premalignant cutaneous lesions, stabilization of the lowest temperature values, standardization of destructive effects, emergence of well-defined and stable changes in the tissues, morphological and histological evaluation, absence of relapses, robust hemostasis during manipulations, histotypic tissue regeneration, and no scar formation. Furthermore, as an increasing rate of premalignant lesions incidence is associated with increasing age, cryosurgery is a considerable choice for elderly patients.

Actinic keratosis. Actinic keratoses (AKs) are keratotic or scaling plaques, macules, or papules characterized by proliferation of atypical epidermal keratinocytes induced by chronic cumulative ultraviolet exposure. Although AKs can undergo spontaneous regression, they are of public health importance due to the potential to progress into invasive squamous cell carcinoma (SCC) with a rate ranging between 0.1% and 20%. As the rate of transformation is difficult to predict, early treatment is highly emphasized. The treatment approaches for AK can be divided into lesion- and field-targeted therapies, but no gold standard treatment has been established to date. Cryotherapy is the most effective and commonly used lesion-targeted first-line approach according to the British Association of Dermatologists guidelines published in 2017 with strength of recommendation A. Being simple and cost-effective, cure rates with cryosurgery are reported to be between 86% and 100% depending on freezing depth, freezing time, the session number, the skill and experience of the physician, the size of the device orifice, the pressure of the cryogen set, the number of lesions, the distance between the lesions, and the presence and size of hyperkeratotic lesions (122).

Evidently, recent technological advances in dynamically evolving cryosurgery have enabled precise, consistent, and predictable therapy to be performed by setting the treatment parameters and therefore allowed to achieve effective and safe results, such as for isolated and mild AK on the face and forearms, as in a study by Ha *et al*. (123) and Ianhez *et al.* (124). Interestingly, it was found that cryosurgery can additionally result in a systemic immunological reaction clearing distant to the treated AK lesion (125). Despite cryosurgery being the mainstay of treatment for isolated AK lesions without any signs of surrounding actinic damage, numerous lesions have been found to render cryosurgery impractical due to the inability to treat the field of cancerization, and other approaches, such as photodynamic therapy (PDT), 5-fluorouracil (5-FU), or imiquimod, can be the top choice rather than cryodestruction (122, 126). Accordingly, as isolated lesions are rarely observed in daily practice, the use of cryotherapy in many patients is limited or even discouraged. The addition of field-directed treatment approaches has been found to overcome this limitation in patients presenting multiple lesions and a wide field of cancerization, resulting in significantly higher patient complete clearance rates, shorter treatment duration, lower recurrence rates, and a smaller number of visits, but may have a higher side effects profile (127-130). From this point of view, an ever-increasing field of research analyzed various treatment approaches combined and evidenced that sequential therapy can provide additional therapeutic benefits and enhance overall AK lesion clearance, especially for recurrent and multiple lesions, including elder patients who show poor cooperation. A recent systematic review and meta-analysis by Heppt *et al.* (131) evidenced the superiority of a combination regimen for AK clearance with equal tolerability. However, further validation is necessary, and this should remain a subject for future high-quality randomized controlled studies, while the suitability of cryosurgery should be decided on a case-by-case basis.

Bowen's disease. Ultraviolet light exposure is also the major etiological factor of Bowen's disease (BD), which is a squamous cell carcinoma *in situ* (SCCis) clinically presented as asymptomatic, well-demarcated, slow-growing erythematous plaque with scale on photo-exposed areas of skin. Although it can behave differently from minimal invasion, partial progression, or spontaneous regression, SCCis has a 3%-5% risk to develop into invasive squamous cell carcinoma, especially among elderly people and immunocompromised individuals. Current research appears to validate cryosurgery as an effective, commonly used treatment option entailing only low costs for single and small cases located in well-healing sites. Overall, findings reveal the feasibility and effectiveness of the approach, specifically excellent healing and no relapse at 12 months' follow-up, but rates vary between different studies due to different techniques and regimens, as well as lesion sizes and locations (132). Clinical clearance of 61% to 100% can be achieved with recurrence rates from 6% to up to 36%. In comparison to other treatment options for BD, cryosurgery results in high clearance rates comparable to curettage, but cryosurgery is significantly more effective (133). Wound healing has been reported to be faster with cryosurgery compared to radiotherapy but slower than cautery plus curettage regimen. Furthermore, ulceration was seen in 25% of cryogenically treated lesions in contrast to 0% with PDT, and the rate of clearance of a single PDT was significantly higher (134). In a comparative study by Park *et al*. (135), the cryosurgery approach was associated with the longest average treatment period, followed by imiquimod, PDT, and excision approaches. The efficacy was highest in the excision arm (100%) and lowest in the PDT arm (62.5%). The imiquimod arm had the highest recurrence rate (33.3%). Importantly, satellite lesions developed in 9% of cryogenically treated patients during follow-up, highlighting the need for careful monitoring.

Owing to the significant variability in clearance, recurrence, wound healing, side effects, and treatment times among different monotherapy approaches, practitioners and clinical researchers extrapolated that the combination treatment of cryosurgery followed by the application of topical immunomodulators, also known as cryoimmunotherapy, can serve the function of achieving

the enhanced therapeutic effect while making shorter total imiquimod or 5-FU bouts and milder undesirable effects of cryosurgery. It has been proposed that cryosurgery can damage the integrity of the stratum corneum in BD, facilitating further penetration of the cream containing imiquimod. Furthermore, the curettage and destructive technique can be varied by using cryosurgery over the curetted region instead of electrodesiccation, eliminating extensive damage to connective tissue. In a study by Nazarali and Sajic (136) that examined the clinical cure rate of combination treatment consisting of cryosurgery followed by a course of topical 5-FU, 229 cases of BD yielded a clearance rate of 90% at 6 months from initial treatment. Similarly, in a study by Soong and Keeling (137), the clinical cure rates were found to be 82% for SCCis. The potential of cryoimmunotherapy to boost the pro-apoptotic, pro-inflammatory, and anti-angiogenic effects of cryosurgery and imiquimod application, resulting in their effective synergism in BD eradication, has also been demonstrated in the Gaitanis *et al.* (138) study. 100% lesion clearance has been achieved with no recurrences observed. The combination of spray with liquid nitrogen and a course of 5% imiquimod cream for histologically confirmed SCCis patients achieved an excellent cosmetic outcome in all cases and a 0% recurrence rate in the MacFarlane and El Tal (139) study. In terms of the combination of the technique involving curettage, followed by cryosurgery using a continuous liquid nitrogen spray, a recent Peikert (140) study showed its promising simplicity, high efficiency, and reliability for select, low-risk non-melanoma skin cancers, as SCCis, with no recurrence. While further validation studies with longer follow-up intervals are awaited, current data support guidelines and recommendations for the management of BD and evidence the synergy of curettage and cryosurgery as cost-effective choice for lesions at good healing sites, which is also comparable to curettage and cautery approaches. However, special attention should be paid to lesions at poor healing sites such as the lower leg, as in these clinical scenarios, curettage and cautery are a better choice compared with cryosurgery in terms of healing time, pain, and recurrence rates with significant differences (141).

Keratoacanthoma. Keratoacanthoma is another example of a rapidly growing, low-grade premalignant condition of pilo-sebaceous and hair follicle units that presents more commonly in the elderly and on sun-exposed areas and closely resembles SCC both clinically and histologically. Although being self-regressing, destructively expanding skin neoplasms with limited growth phase followed by complete involution of tumor tissue, their evolution process is unpredictable and can result in dysmorphic, potentially mutilating scars. Importantly, the possibility of missing SCC prompts management intervention for all patients with this premalignant condition. Among different invasive therapeutic approaches, minimally invasive cryosurgery can be an effective option to promote spontaneous regression of keratoacanthoma, resulting in a cosmetically better scar (142). Supportive findings were demonstrated by a Sinjab (143) study using liquid nitrogen application after previous tangential curettage of skin lesions, when all patients showed relief of disease, no recurrence, and only a few side effects. The approach has also demonstrated its effectiveness, safety, and feasibility using an open liquid nitrogen spray in combination with intralesional methotrexate and imiquimod in a Gaitanis and Bassukas (144) study that resulted in sustained clearance after 6-24 months follow-up. A study by Panagiotopoulos *et al*. (145) combined curettage, electrodessication, and cryosurgery and achieved a success rate of 97.8% with an excellent cosmetic outcome. No infections or serious adverse events have been reported.

Lentigo maligna. Lentigo maligna is a melanocytic neoplasm with an incidence that has increased dramatically during the past decades. Clinically, it is an acquired pigmented macule that occurs on the sun-exposed skin of middle-aged or elderly individuals and, if untreated, with a 5-50% risk progresses to invasive lentigo maligna melanoma. Evidently, modern cryosurgery has demonstrated its effectiveness, producing satisfactory

therapeutic and cosmetic results without recurrence, specifically in the treatment of elderly patients with high-risk or lesions not easily amenable to surgery (146-148). Cryosurgery with a nitrogen liquid spray resulted in complete clinical resolution of lesions with no recurrence or metastasis during a follow-up of 5 years. Additional evidence from the Kuflik and Gage (149) study on lentigo maligna treated with liquid nitrogen delivered by open spray has been favorably comparable to excisional surgery, providing excellent cosmetic and curative results. A 6% rate of recurrence at 3-year follow-up was observed, which was successfully eliminated by re-treatment. Cryoimmunological treatment of cryotherapy with imiquimod application in lentigo maligna lesions has also proposed encouraging results with a lesion-free patient for 26 months after the treatment (150). Although the rate of recurrence after cryosurgery in the literature varies between 0% and 36%, a recurrence is comparable to other treatment options and can be successfully retreated with cryosurgery in most instances, as well as potentially reflecting a wide range of cryosurgery approaches, including old ones, with different freezing parameters.

Chronic radiodermatitis. Radiotherapy as an essential component in many cancer treatment and palliation protocols is still strongly associated with the development of skin toxicities. Late reactions leave chronic results, namely chronic radiation-induced dermatitis, a permanent and potentially irreversible condition that can and progress to ulceration, tissue necrosis, and *de novo* cutaneous malignancies. Notably, professionals also frequently face chronic dermatitis due to the absence of any protection several decades ago. Promising results have been shown with cryosurgery, and most importantly, on chronic radiodermatitis located on fingers. A study by Conejo-Mir *et al*. (151) demonstrated excellent results on professional chronic radiodermatitis with incipient pretumoral lesions using both spray and a probe cryosurgery. Presentation of finger function and mobility has been achieved in all cases 2 months after treatment, and no recurrence has been observed after two years of follow-up.

Porokeratosis. Porokeratosis is another precancerous skin condition characterized by multiple annular hyperkeratotic lesions, which has been suggested as a potential target for cryosurgery. Recent research has shown partial to complete response rate in multiple clinical variants of porokeratosis, including disseminated actinic superficial porokeratosis, porokeratosis of Mibelli, linear porokeratosis, and genitogluteal porokeratosis (152). In a study by Bianchi *et al.* (153) comparing cryosurgery using a contact cryosurgical unit, photodynamic therapy with methyl aminolevulinate, and imiquimod 5% cream, the former demonstrated superiority in the treatment of disseminated superficial actinic porokeratosis, with 80-100% of lesions completely resolved after a single course of therapy. Supportive findings were reported by Dereli *et al.*'s (154) study in the treatment of porokeratosis of Mibelli using liquid nitrogen spray cryosurgery, as superiority to other destructive methods was identified, including advantages such as high cure rates, simplicity, low cost, short treatment period, and fewer complications. Porokeratosis plantaris discrete, usually resistant to conservative management, has also been successfully treated cryosurgically with a cure rate of 90.5% (155).

Malignant Cutaneous Lesions

Cryosurgery has not yet gained widespread recognition as a first-line treatment approach in malignant lesions, but multiple studies in the clinical setting have undoubtedly evidenced its capability to induce natural immuno-stimulating effects, complete ablasticity, and organotypic regeneration while having almost no complications, differing favorably from and putting itself above all known methods of active treatments (156).

Cutaneous melanoma. Malignant melanoma. The transition towards significantly older populations and elevated occupational and recreational UV light exposure in recent decades have raised major concerns due to the associated steadily increasing incidence and prevalence of skin cancer, with an annual increase in melanoma of 4-6%, and

a lack of efficient management approaches to alleviate the increased burden. Melanoma, as a malignancy derived from the malignant transformation of melanocytes, is the most aggressive and lethal form of cutaneous neoplasm, resistant to traditional therapies, especially due to its rapid capability to spread locally, regionally, and distantly into almost all organs. According to an ever-increasing body of international research and medical cryology experts, cryosurgery's ablastics and feasibility of application in anatomically inaccessible places are best manifested in treating primary cutaneous malignant melanoma and its metastases from stages II-IV. The superior outcomes achieved from low-temperature exposure are primarily due to the establishment of conditions aiding rapid fixation of melanoma cells and their further devitalization, resulting in a complete and irreversible necrosis of the entire volume of tumor tissue (157). Importantly, cryodestruction can bring the effect of potentiation and provide initial ablasticity to the whole treatment schedule when applied in combination with radiotherapy, regional, or systemic chemotherapy, specifically expedient in conditions of the disseminated process.

In a case study of a 101-year-old patient with advanced malignant melanoma of the facial skin treated with liquid nitrogen and nitrous protoxide cryoprobes, the outcomes corroborated the findings of a great deal of the previous research by demonstrating well tolerability, good aesthetic results, and recurrence- and distant-disease-freedom at 2-year follow-up (158). Appropriately highlighting the feasibility of cryosurgery in the treatment of elderly and high-risk surgical patients with lesions in anatomically critical sites, avoiding skin flap transposition for tissue repair and complications, while achieving satisfactory functional and oncological outcomes.

Inoperable melanoma metastases. Cutaneous melanoma treated primarily with excision of the primary lesion can recur as multiple in-transit metastases, including both satellite deposits and true 'in-transit metastases', and is generally associated with a poor prognosis while potentially limb-threatening, disabling, and frightening to patients. Evidently, the principal aim of the treatment of this condition is palliation using local ablative techniques (159). Cryosurgery is an effective method that obtains good to excellent local control, which, besides the direct ablative effect, can potentially stimulate an immunological response and therefore enhance the effectiveness of the treatment. In a study by Tarkowski *et al.* (160), patients treated with liquid nitrogen cryosurgery devices were metastases-free at the end of the therapy; no distant metastases were observed and, as well, no major comorbidities were noted. Nevertheless, the successful outcomes observed in the vast majority of research studies on the topic are mostly a synergistic effect of cryosurgery and systemic immunotherapy. This is achieved by the production of local necrosis of malignant cells and induction of a systemic anti-tumor immune response by cryosurgery that is further enhanced with the immunostimulatory, proapoptotic, and antiangiogenic effects of immunotherapy, which may also protect against regional lymph node metastases. Supportive findings were reported by the Gonzalez-Cardona and Rueda Cadena (161) study on a 62-year-old patient diagnosed with an ulcerated acral lentiginous melanoma, stage IIID disease, and having locoregional progression treated with cryosurgery and nivolumab in an attempt to achieve regional control. Cryosurgery showed as an affordable adjuvant treatment with satisfactory clinical response, namely: disappeared in-transit cutaneous metastases and regained function of the limb. Similarly, in a Rivas-Tolosa *et al.* (162) study on inoperable locoregional cutaneous metastases of melanoma treated with cryosurgery and topical 5% imiquimod, therapy achieved a 65% response, where 40% of these patients had complete remission and 25% had partial response. Systemic disease progression has been observed in 80% of patients. Overall, this synergetic approach was simple to apply, had minimal adverse effects, and achieved response rates similar to other, more complex treatment options. In another retrospective study by Moreno-Ram Irez *et al.* (163) on patients with cutaneous metastatic melanoma treated with cryosurgery and topical 5% imiquimod, 40% of patients

experienced complete remission of metastatic lesions while 35% of patients had locoregional progression.

Basal cell carcinoma. In the case of non-melanoma skin cancer, cryosurgery is one of the established effective therapies for basal cell carcinoma (BCC), with a high cure rate of 94% to up to 99% at 5-year follow-up yielding favorable functional and cosmetic results and low recurrence rates, shorter healing time, less scarring, and fewer adverse effects (164-168). Therapeutic success with this malignant tumor arising from abnormal, uncontrolled growth of basal cells is of special importance due to its continuously growing incidence and the fact that it is the most common form of all malignant neoplasms, which can cause significant local destruction and morbidity if not adequately treated.

According to the best evidence, sufficient data allow to consider cryosurgery as a reasonable treatment for BCC with effectiveness comparable to other treatment options, but on the condition that patients are correctly classified with strict diagnostic criteria and the standardized procedure is performed by a trained operator with adequate peripheral margins. Specifically, a histologic cure of liquid nitrogen cryosurgery has been successfully shown in superficial, low-risk, well-defined, noduloulcerative BCCs of the trunk and extremities less than or equal to 1 cm (169, 170). Preliminary findings suggest cryosurgery as an effective treatment option for small- and medium-sized, well-defined medium-aggressive, and large clinically well-defined Glas II BCCs for selected patients (171, 172). One remarkable example of cryosurgery application is in cutaneous BCC of the head and neck. In a study on this group of population with relapsing tumours after failure of preceding treatment modalities, Hu *et al.* (173) found cryosurgery to be an effective method causing minimal surgical trauma and violation of normal physiology while significantly preserving tissue regeneration potential and allowing optimal recovery of anatomical features and functions, in addition to almost invisible and soft resulting scars. Better long-term clinical and aesthetic results were observed in lesions <1 cm in size with clear boundaries. Liquid nitrogen cryosurgery has also been reported to successfully treat high-risk sites as vulvar BCC (174). Cryosurgery using a nitrous oxide probe has certain advantages over surgical removal of BCC of up to 8 mm in diameter in the periocular region, but careful inclusion criteria analysis and follow-up is advisable due to a recurrence rate of 8% (175).

Importantly, cryosurgery can be designated for the elderly population of patients, for those that preclude the use of surgery and with multiple comorbidities that are subject to possible difficulties in healing, wound infection, and failure of skin grafts (176). Supportive findings have been demonstrated by Har-Shai *et al.* (177) in elderly patients with nodular or superficial BCCs of the lower limbs and associated comorbidities. Complete destruction of the tumor has been achieved by intralesional cryosurgery in all cases with no evidence of wound infection or recurrence. A cure rate of around 95% with an excellent clinical response with complete healing, satisfactory functional and cosmetic results, and good patient tolerance has been reported in elderly patients with BCC (178).

Tissue destruction can be increased by synergy of cryosurgery and the administration of imiquimod, also known as cryoimmunotherapy, by means of firstly elevating tumor vascular permeability by cryosurgery and, as a result, facilitating the penetration of imiquimod that modifies the immune response and stimulates apoptosis in BCC cells. In 2011, MacFarlane *et al.* conducted a retrospective study that revealed clinical improvement with reduced lesion size, mild side effects, and a recurrence of 2% (a liquid nitrogen session followed by a 6-week course of imiquimod) (139). There was additional evidence from the Nakuci and Bassukas (179) study that recorded high cure rates and therefore the feasibility and efficiency of the combined protocol (daily imiquimod for five weeks and a liquid nitrogen cryosurgery session at the end of the 2nd week) that is applicable for the treatment of primary and relapsed BCC. Another study reported histologically confirmed clearance of the lesion in a patient with a nodular BCC on the nose who was treated with a liquid nitrogen session followed by imiquimod cream for

6 weeks. On the other hand, Gaitanis *et al*. (180) evidenced significantly superior tumor clearance and overall treatment efficiency when cryosurgery is applied two weeks after the imiquimod course compared to cryosurgery applied prior to the initiation of a 5-week daily imiquimod course. Other perspective combinations that revealed complete response and a good cosmetic outcome with minimal side effects were combinations of cryosurgery with topical 5-fluorouracil (5FU) (181). Combined curettage and cryosurgery with standardized protocols is another option that achieves excellent clinical clearance rates for BCCs with nodular features (182).

Squamous cell carcinoma. Cutaneous squamous cell carcinoma (cSCC) is the second most frequent cancer, which usually behaves as an invasive malignancy prone to metastases, with dramatically increased incidence from 50% to 300% and mortality rates in the last three decades. Being a member of the non-melanoma skin cancer group together with BCC, cSCC originates from the malignant proliferation of epidermal keratinocytes from precursor lesions such as squamous cell carcinoma *in situ* (SCCIS) and actinic keratoses. While electrodesiccation with curettage and surgery are the cornerstones of the management of cSCC, research has identified that not all tumours are easily resectional and that significant recurrence can range from 3.5% to up to 28.0%, which creates associated treatment challenges and economic burden. However, considering that cutaneous cancer is the fifth most expensive malignancy to treat, novel and multidisciplinary approaches have been proposed.

According to publications dated back to 1988 and 1991, cryosurgery has been shown to be a safe, well-tolerated, and cost-effective method in the treatment of selected non-melanoma skin cancer, as cSCC, producing excellent cosmetic results with a 5-year cure rate of 97%. Cryosurgery has been found to favorably compare with other established methods of therapy, with recurrences seen in 2.9% of treated cases (183). Importantly, evidence gained from recent research has shown that both superficial and large SCC can be successfully treated by open-spray cryosurgery and intralesional cryosurgery, respectively. In a study by Lee *et al*. (184), nodular SCC has been treated with intralesional cryosurgery, which allowed tumor reduction from 40% to 75% in size within one week, and complete remission was observed in 100% of tumors in two months. High patient satisfaction has been noted, and no patient experienced wound infection after the procedure, required analgesics, or experienced recurrence during follow-up (average 5.1 years).

Soft tissue sarcoma. Kaposi sarcoma (KS) is an angio-proliferative malignancy of endothelial cells that primarily effaces the skin and internal organs and is mediated by human herpesvirus-8 (HHV-8). There are four distinct variants of KS: classic, endemic, epidemic, and iatrogenic. In classic-type, the malignancy remains superficial and has a slow progression, whereas iatrogenic-type, as the most prevalent, is associated with immunosuppression mostly among advanced human immunodeficiency virus (HIV) patients and represents a progressive disseminated disease. While treatment choice depends on KS variant, a patient's comorbidities, and level of involvement, multiple treatments have been attempted, but an optimal therapy is yet to be identified. Generally, local treatment approaches are preferable in classic-type KS limited to the skin, including radiotherapy, cryosurgery, laser therapy, surgery, and intralesional immunosuppressive drugs. Systemic treatments, such as bleomycin, liposomal daunorubicin, and IFN-alpha, may be the best approaches for progressive disseminated disease.

Current research appears to support the evidence that cryosurgery is the preferred first-line treatment of small superficial KS lesions or those located at different anatomical sites with an overall response rate and short-term cure rates of 70-90%. However, the approach is not suitable for widespread lesions considering side effects associated with cryosurgery such as pain and erosions. Evidence from the Tappero *et al.* (185) study on cutaneous lesions of KS associated with acquired immune deficiency syndrome (AIDS) has also shown that liquid nitrogen cryosurgery can result in a complete response in 80% of

treated lesions that lasted a minimum of 6 weeks. The therapy was well-tolerated, and no secondary infections occurred. Furthermore, cryosurgery is advisable for KS lesions that show incomplete cosmetic improvement with systemic therapies. Supportive findings were reported by the Kutlubay *et al*. (186) study that treated KS lesions with liquid nitrogen and achieved complete response in 63% of patients with no recurrences or secondary infections. Similarly, a case report by Doupis *et al*. (187) of an 87-year-old patient with a rare B-cell chronic lymphocytic leukemia (CLL) and cutaneous KS revealed a positive outcome, namely: a complete tumor removal and wound healing and a good cosmetic result, along with method simplicity and safety. The application of cryosurgery in conjunction with other modalities has also demonstrated efficiency, tolerability, technical safety, and feasibility in the treatment of patients with soft tissue sarcomas, including KS (188). A study by Gu *et al*. (189) assessed KS patients with classic, HIV-associated, or HIV-negative types who received combination therapy of cryosurgery followed by topical imiquimod. This synergy allowed to achieve complete resolution in 93% of lesions and 89% of patients during a follow-up of 58 weeks with no infections, highlighting its efficacious potential and comparatively low-risk treatment for limited cutaneous KS lesions. In the case of the patient with nodular HIV-associated KS of the foot who had not been responsive to any of the typical HIV-associated KS therapies and was not a good candidate for surgical excision or radiation therapy, a combination of intralesional bleomycin and cryosurgery resulted in lesions resolution, and the patient regained his ability to perform functions of daily living (190).

Conclusion

Amid the complex and frustrating challenges posed by the global burden of skin and subcutaneous diseases–compounded by significant psychiatric and psychological impacts–cryosurgery has emerged as a valuable treatment option across a range of benign, premalignant, and malignant conditions. Innovations in science and technology have steadily advanced cryogenics to provide safe, effective solutions for this diverse category of diseases. While current evidence on cryosurgery is promising and highlights its functionality and outcomes, available research remains limited, often relying on older, short-term findings from single-case reports. There is a need for larger, multicenter randomized controlled studies with extended follow-up periods to solidify existing knowledge, validate safety, cost-effectiveness, and effectiveness relative to other treatments, and support its inclusion in primary clinical guidelines and recommendations.

To advance this field, it is critical for clinicians and researchers worldwide to collaborate, share advancements, and develop trials that confirm repeatability and build confidence. Special attention should also be directed toward establishing and supporting local residency programs to facilitate this research and foster expertise in cryosurgery.

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Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, A.K., HJ; writing–original draft preparation, A.K., HJ; writing–review and editing, A.K., H.J., and R.M.; visualization, A.K., H.J., R.M., K.M., H.G., and J.T.; funding acquisition, H.J. All Authors have read and agreed to the published version of the manuscript.

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