Cryosurgery

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Key Points

Cryodestruction by liquid nitrogen is a very efficient method of treatment for various benign and malignant skin conditions. Proper planning of freezing and assessment of depth by monitoring the halo around the spray freeze or cryoprobes technique can successfully ablate many suitable lesions. Complications are minimal, no anesthesia is necessary, and the cost is low.

Table 114.1 Terminology of using subzero temperatures in biology and medicine

Cryobiology	Effects of subzero temperatures on a living system
Cryogenics	Development of freezing temperatures within a living tissue or cell
Cryotherapy	Therapeutic use of cold in a wide sense
Cryosurgery	Well-aimed and controlled destruction of disease tissue by application of cold

Modified from Zouboulis (1999)

General Principles

Cryosurgery refers to well-aimed and controlled application of freezing temperatures for the destruction of diseased tissue (Table 114.1) (Zouboulis 1999). Although primarily used for cutaneous lesions, cryosurgery is now getting wider applications in gynecology, urology, ophthalmology, neurosurgery, cardiology, and oncology. Since the discovery of liquid nitrogen in the 1940s, the modern era of cryosurgery has begun with myriad of procedures being performed in the outpatient settings with high safety and effectiveness, low cost, ease of application, good cosmetic results, and no need for local anesthesia.

History

Cryosurgery has been used in dermatology for the last 150 years. The first attempts were to treat lesions of lupus vulgaris (skin tuberculosis) with cold ice. Later on liquid helium, liquid air, and liquid oxygen were used, especially upon discovery of the vacuum flasks to store cryogens by James Dewar at the end of the nineteenth century. The ideal cryogen, liquid nitrogen, once discovered in the 1940s, quickly gained popularity by having the lowest boiling temperature of

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−196 °C and being noncombustible. The initial application with cotton-ball method, preferable in the early 1950s, soon revealed inefficient due to the inability to achieve complete and optimal freezing of below −20 ° C at the treatment site. In the early 1960s, numerous sophisticated devices have been developed not just to preserve and deliver cryogen in the spray or contact technique, but also to monitor the temperature inside and below the treated lesions provided controlled and reliable cryodestruction of the targeted lesion. The works of dermatologist Setrag Zacarian and engineer Michael Bryne from Connecticut pioneered the use of cryogen spray units, now widely used for the application of cryosurgery worldwide.

Mechanism of Action

The biological changes that occur during the freezing process are divided to three phases, (a) direct tissue (cell injury), (b) vascular phase (vessel injury), and (c) inflammatory (immunological) phase, which is recently getting more and more attention due to the effects of improving antigen presentation in the frozen tissue and stimulation of the protective immune response.

(a) *Direct Cell Injury* – The initial drop of the temperature by rapid freezing speed of 100 °C/min first produces extracellular ice and cell dehydration (which is potentially reversible) also known as *heterogeneous nucleation*. Further freezing results in the formation of intracellular ice, since dehydrated cells open aquaporins, special channels in the cell membrane to fight the dehydration and improve water balance. The size of the ice crystals is very important, since larger crystals formed by rapid temperature decrease have more damaging effect. Intracellular ice crystals damage the mitochondria, endoplasmic reticulum, and other cell organelles inducing irreversible cell destruction also known as *homogenous nucleation*. This phase occurs when temperature drops below −20 to −25 °C, for keratinocytes, but much sooner for melanocytes (−4 to −7 °C) and sebocytes and hair follicles (−15 °C). Hence, the cryosurgery on hairy areas or pigmented skin can result in permanent alopecia or hypopigmentation, respectively. *Tissue thawing* at slow speed (spontaneously or up to 10 °C/min) contributes to more volume changes and intracellular edema due to the reversal of the osmotic gradient as well as intracellular water recrystallization. Thawing time should be at least 1.5 times longer than the freezing time for adequate cryosurgery. Fibroblasts die at −30 to −35 °C and are more resistant to freezing. That is why cryodestruction of malignant tumors requires −50 °C of freezing temperatures for the complete damage of tumor cells and its stroma, while benign lesions for optimal treatment need much lower freezing for −20 to −25 °C where just destruction of keratinocytes is sufficient without the destruction of the collagen supporting network. Furthermore, the preservation of stroma in cryodestruction of benign lesions is responsible for the lowest incidence of keloids in cryosurgery in comparison to any other surgical modality. The effect on cell viability reaches maximum at approximately 100 s of freezing, so the *optimal duration of freezing* is up to 30 s for benign lesions and 60 s for malignant tumors. A *second freeze-thaw cycle* causes more cell death and is required when malignant tumors are treated; for benign lesions, on the contrary, it is not essential. The treatment time of 30 s usually forms epidermo-dermal separation and hemorrhagic blister but never produces scarring or keloids. On the contrary, 60 s freezing (desirable for malignancies) results in cryonecrosis and formation of a scar.

(b) *Vascular Phase* – Cryogenic injury produces significant vascular changes including stasis, tissue anoxia, edema, focal capillary damage, hemorrhage, and microthrombosis. Thrombosis of all vessels is seen when temperature drops to −15 to −20 °C.

(c) *Immunological* (*Inflammatory*) *Phase* – An immunological response to cryosurgery was suggested in the late 1960s. This area is now

experiencing a great deal of research. The fact that the frozen tumor remains "in situ" after cryoablation enables macrophages, neutrophils, and dendritic cells to infiltrate in the first 48–72 h attracted by the cytokine milieu produced by cryodestructed cells. Later, lymphocytes migrate into the area contributing to augmentation of the immune response. Recent papers have suggested the stimulation of "protective response" after cryodestruction with suppression of T-reg lymphocytes, which are crucial for tumor survival and its escape from the host immune system. The evaluation of methods of augmenting the protective immune response after cryoablation with the use of adjuvants like imiquimod or cytotoxic compounds like podophyllin is currently also undergoing intensive investigation.

Equipment

Cryosurgery equipment (Fig. 114.1a–d) consists of cryogen liquid and its container, cryogun with different cryoprobes, spray tips, and attachments for intralesional cryosurgery – Luer lock and acne aperture for cryopeel. Liquid nitrogen is the ideal cryogen due to its very low boiling point of −196 °C (Table 114.2). The maximum storage

Fig. 114.1 Cryosurgery equipment. (**a**) Cryogun, withdrawal tube and container, (**b**) extensions for open spray, (**c**) Luer lock for intralesional cryosurgery, (**d**) acne aperture for cryopeel

Table 114.2 Cryogens and boiling points

Liquid nitrogen	−196 °C
Carbon dioxide	−70 °C
Nitrous oxide	−60 °C
Fluorocarbon liquids	−90 °C

capacity for containers used in skin surgery procedures is up to 50 l and for the time period of up to 300 days. The liquid nitrogen is poured into the cryogun, i.e., spray unit by using withdrawal tube (fills one bottle at the time) or withdrawal device (fills several bottles at the time). Simple decanting is to be avoided due to the risk of cryogen spillage and burns. Liquid nitrogen is odorless, inert, noncorrosive, noninflammable, and colorless and, at the room pressure of 1 atm, has temperature of 195.8 °C. Cryoguns can vary in volume from 300 to 500 ml and can store liquid nitrogen from 12 to 24 h. Simple Q-tips and plastic containers could be used for spot freeze technique with a cotton ball. This method is not precise and often does not produce complete freezing beyond desirable plateau for the treatment of benign tumors, which is below −15 °C. The used cotton ball should never be redipped into the spray bottle due to the risk of the contamination. The cryogen should be poured in the plastic/paper container to be discarded after each patient. The nozzles sizes for the spray bottle range from A through F, with F representing the smallest aperture. Different cryochambers, cryocones, and cryoprobes are used for more focused freezing when limited effect of the spray bottle is desired, without risk of damaging the sensitive surrounding skin. Bended extensions are attached to the spray nozzle to provide focused and precise application of the cryogen to cavities like the oral cavity, lips, ears, or nostrils. The variety of cryoprobes used for contact cryosurgery should be matched with the size of the treated lesions. Finally, Luer lock adapter serves for the attachment of the 16 or 18 G needle for intralesional cryosurgery mostly for keloids and some tumors. The last part of the equipment are tissue temperature monitors, obligatory with cryodestruction of malignant tumors, which work based on temperature change, electrical impedance, or ultrasound transmission. Finally, the invention of a new device – Cry-Ac Tracker (Fig. 114.2) – facilitated the controlled timely destruction of the target tissue by using the infrared monitoring method.

Fig. 114.2 Cry-Ac Tracker with infrared monitoring device

Techniques (Fig. 114.3)

The dose of liquid nitrogen and the choice of delivery method depend on the size, tissue type, and depth of the lesion. The area of the body on which the lesion is located and the required depth of freeze also should be considered. Additional patient factors to consider include the thickness of the epidermis and underlying structures, the water content of the skin, and local blood flow.

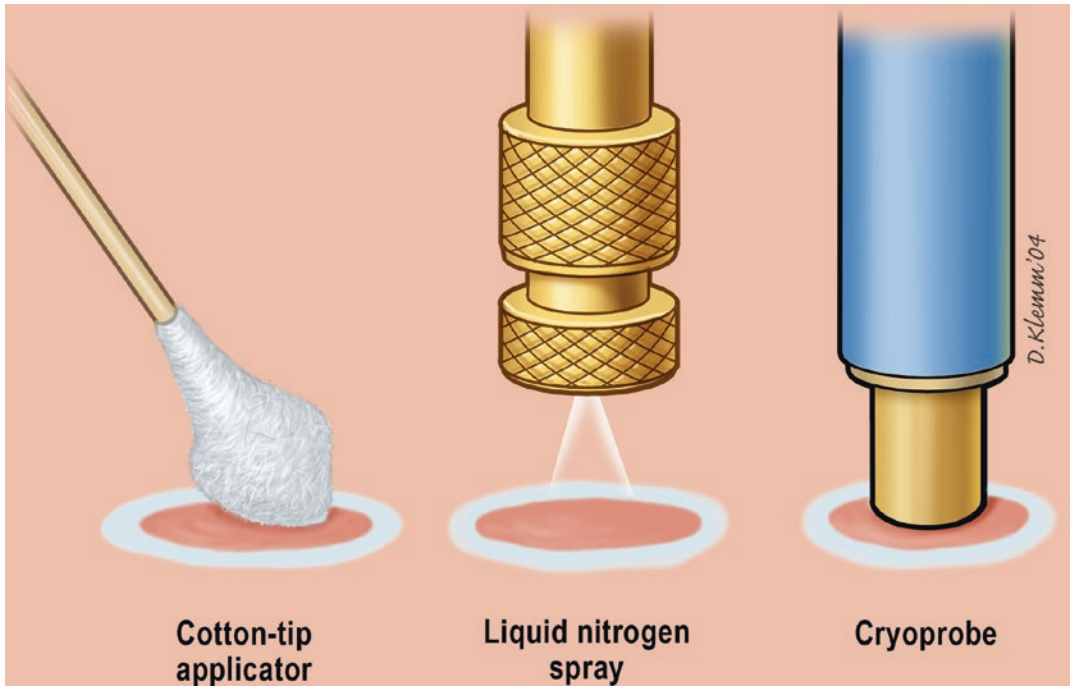

Fig. 114.3 Cryosurgery techniques (Printed with permission – Copyright David Klemm)

Liquid nitrogen spray methods for lesions of different sizes include the timed spot freeze or direct spray technique, the rotary or spiral pattern, and the paintbrush method, confined spray technique, and contact and intralesional cryosurgery (Fig. 114.4a–c). Each modality has different maximal freezing temperatures achieved in the treated tissue and should be used according to the desired depth of freeze (Table 114.3).

(a) *Timed Spot Freeze (Open Spray Technique)*. It may be the most appropriate method for physicians who are learning to perform cryosurgery. Use of this technique maximizes the ability to destroy a lesion with minimal morbidity. The freezing time is adjusted according to variables such as skin thickness, vascularity, tissue type, and lesion characteristics. Nozzle sizes B and C are suitable for the treatment of the most benign and malignant lesions; they are the apertures most frequently noted in case reports.

For the standard spot freeze technique, the nozzle of the spray gun is positioned 1–1.5 cm from the skin surface and aimed at the center of the target lesion. The spray gun trigger is depressed, and liquid nitrogen is sprayed until an ice field (or ice ball) encompasses the lesion and the desired margin. The designated ice field may need to be delineated in advance with a skin marker pen, because freezing may blur pretreatment lesion margins. The margin size depends primarily on the thickness of the lesion and whether the lesion is benign or malignant. Margins for most benign lesions are 1–2 mm beyond the visible pathologic border. Premalignant lesions need margins of 2–3 mm, while malignant lesions require margins of 5 mm of clinically normal skin to ensure adequate removal. These margin sizes allow enough depth of freeze to ensure temperatures of −50 °C to a depth of 4–5 mm. For benign/premalignant lesions freezing down to −25 °C is sufficient (Table 114.4). Once the ice field has filled the specified margin, the spray needs to be maintained (intermittently pressing/depressing the trigger) with the spray canister trigger pressure

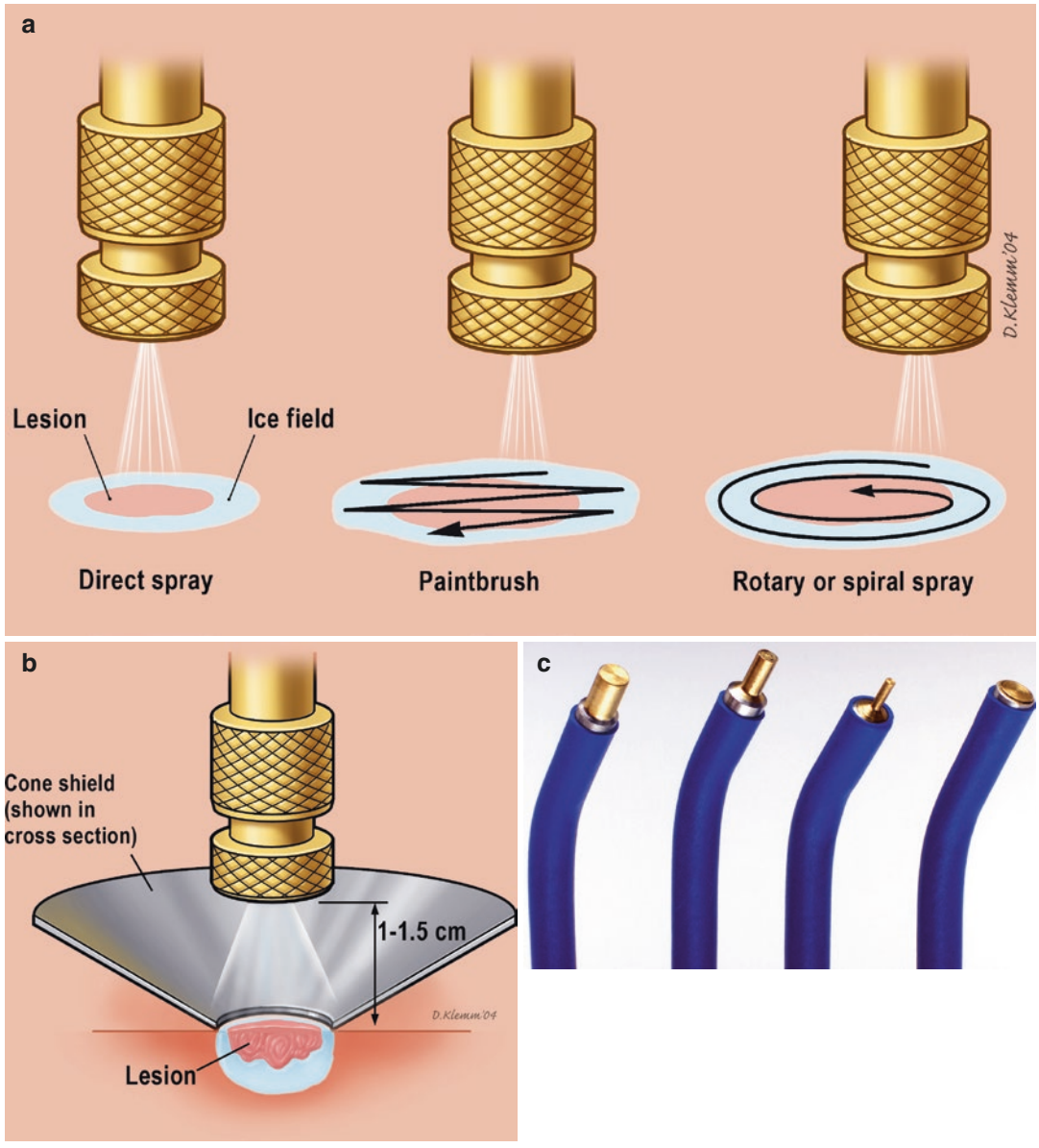

Fig. 114.4 (**a**) Spray patterns for larger lesions, (**b**) confined spray technique, (**c**) cryoprobes for contact cryosurgery (Printed with permission – Copyright David Klemm)

Table 114.3 Surface tissue temperatures attainable with various cryogens

Cryogen	Temperature (°C)
Carbon dioxide snow	−79
Nitrous oxide	−75
Liquid nitrogen Q-tip	−20
Liquid nitrogen spray	−180
Liquid nitrogen probe	−196

and, thus, the liquid nitrogen spray flow adjusted to keep the target field frozen for an adequate time. This time may vary from 5 to 30 s (60 s for malignant tumors) beyond the initial time for the formation of the ice field. If more than one freeze-thaw cycle is required for lesion destruction, complete thawing should be allowed before the next cycle. The

Table 114.4 General cryosurgical settings for skin tumors

Parameters	Benign	Malignant
Freezing speed	Moderate (≤100 °C) or rapid (≥100 °C)	Rapid (≥100 °C)
Thawing speed	Slow (10 °C/min) or spontaneous	Slow (10 °C/min) or spontaneous
Osmotic phenomena	Homogeneous and heterogeneous nucleation	Homogeneous nucleation
Probe temperature	−86 to −196 °C	−196 °C
Duration	30 s	60 s
Repetition of freeze-thaw cycles	No	Yes (twice)
Vascular reaction	Yes	Yes
Immunological reaction	Probable	Probable

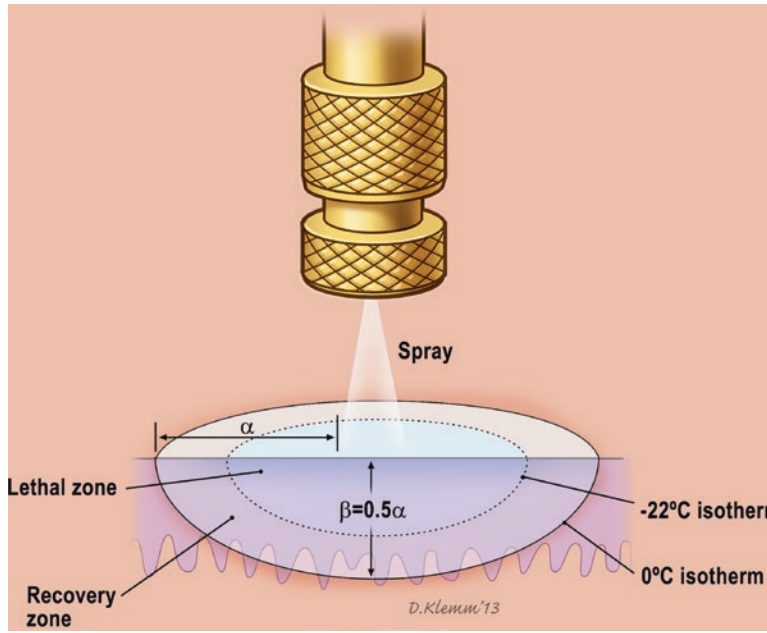

Fig. 114.5 Depth of freeze in open spray technique (Printed with permission – Brymill Corporation Inc.)

depth of freeze is approximately half of the lateral ice ball radius (Fig. 114.5). The thawing time is usually 2–3 min, i.e., 1.5 to two times longer than the freezing time. For lesions bigger than 2 cm in size, the open spray technique can be modified into the *rotary, spiral, or paintbrush pattern* to allow complete freezing.

(b) *Contact Cryosurgery*. Cryoprobes attached to liquid nitrogen spray gun can provide additional versatility especially when dealing with smaller and delicate lesions where deeper penetration is necessary (hemangiomas) or when surrounding skin is to be minimally affected like eyelid margins. The cryoprobes can vary in shape and size and are applied directly to the skin, ablating the lesions with contact exchange of the heat, and can be used with contact gel. The separate small hose is releasing liquid nitrogen from the side of the probe and should be kept away from the skin to avoid spillage of cryogen to nondesirable areas. Contact cryosurgery can penetrate up to 20 mm in depth and requires double freezing

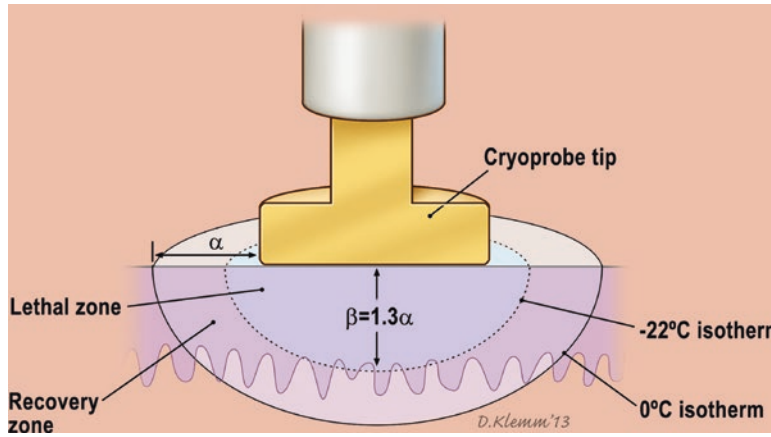

Fig. 114.6 Depth of freeze in contact cryosurgery (Printed with permission – Brymill Corporation Inc.)

times compared to spot spray freeze technique. The depth of freeze is approximately 1.3 times the radius of the ice ball (Fig. 114.6).

(c) *Intralesional Cryosurgery*. Needles for intralesional cryosurgery are applied to the nozzle using Luer lock adapter. A sprayed cryogen is then passed through the needle forming the ice cylinder. The distance of freeze can be estimated by monitoring the degree of extension of the whitish ice ball around the points of contact between the skin surface and the visible part of the needle. Depending of the size of the lesion, the needle can be reintroduced several times in order to provide more complete freezing. The main advantage of intralesional technique is the ability to freeze deeper than 20 mm, which is the maximal limit for spray and contact methods.

Clinical Applications

Most benign skin lesions can be treated successfully with any of several treatment modalities (excision, cryosurgery, electrodesiccation, and curettage). However, cosmesis, cost, and patient convenience may make one treatment modality more desirable than another. Patients should be informed about all treatment options and should be allowed to choose from the reasonable alternatives. Cryosurgery has advantages over the other modalities. Preparation time is short, and treatment requires no expensive supplies or injectable anesthesia. In addition, the risk of infection is low, wound care is minimal, and suture removal is not needed. Correct clinical diagnosis and lesion selection are as critical as the timing of the liquid nitrogen spray in producing a favorable outcome. Depending on the type of lesion, standard technique may need to be modified. Smaller flatter lesions require only 5–10 s of freezing and one cycle only. Larger thicker lesions may require longer duration of freeze up to 20 or even 30 s. Superficial keratin, especially in plantar warts, is a good insulator and should be removed by paring the lesion or application of keratolytics like salicylic acid in 2 weeks prior to cryosurgery. Before deciding about the length of freeze, one should always keep in mind the individual sensitivity of the different cell types to low temperature and adjust the duration of destruction (Table 114.5). Table 114.6 summarizes cryosurgery techniques for a variety of skin lesions.

Table 114.5 Sensitivity of different cell types to cryoinjury

Melanocytes	−4 to −7 °C
Sebaceous glands and hair follicles	−20 °C
Keratinocytes	−20 to −30 °C
Fibroblasts	−30 to −35 °C
Benign tumors	−20 to −25 °C
Malignant tumors	−50 to −60 °C

Table 114.6 Cryosurgery indications and techniques

Indications	Freeze time (seconds)	Number of freeze-thaw cycles	Margin (mm)	Typical treatment regimen	Technique
Benign lesions					
Acne	5–15	1	1	Once	Cryopeel
Angioma	10	1	<1	Once	P
Cutaneous horn	10–15	1	2	Once	OS
Dermatofibroma	20–60	1–2	2–3	Twice, bimonthly	P/OS
Hypertrophic scar	20	1	2	Once	OS/P
Ingrown toenail	30	1	2	Twice, bimonthly	OS
Keloid	30	1–3	2	Three times, bimonthly	OS/P
Myxoid cyst	20	1	<1	Once	OS/P
Molluscum contagiosum	5–10	1	<1	Twice, monthly	
Oral mucocele	10	1	<1	Once	P
Pyogenic granuloma	15	1	<1	Once	OS
Sebaceous hyperplasia	10–15	1	<1	Variable	P
Seborrheic keratosis	10–15	1–2	<1	Once	
Skin tags	5	1	1	Once	F/OS
Solar lentigo	5	1	<1	Once	OS
Warts	10–60	1–2	2–3	Three times, monthly	
Premalignant lesions					
Actinic keratosis	5–20	1	<1–2	Usually once	OS
Bowen disease	15–30	1–2	3	Three times, monthly	OS
Keratoacanthoma	30	2	5	Usually once	OS
Malignant lesions					
Basal cell carcinoma	60–90	2–3	5	Usually once	OS
Kaposi sarcoma	20–40	1–2	3	Three times, monthly	CP
Lentigo maligna	60	2	5	Usually once	OS
Squamous cell carcinoma	60–90	2–3	5	Usually once	OS

By convention, freeze time is given as the interval following visible white ice formation
OS open spray, *P* cryoprobe, *F* forceps

Malignant conditions (mostly superficial basal cell carcinoma) require 60 s of freeze, tissue temperature monitoring, and two freeze-thaw cycles (Table 114.7).

Complications, Side Effects, and Contraindications

Contraindications

The relatively few contraindications to cryosurgery generally are related to concomitant illnesses in which excess reactions to cold may occur or delayed healing may be anticipated (Table 114.8). Some relative contraindications may make alternative treatment modalities more suitable. Physicians often do not perform cryosurgery in the pretibial areas, especially in elderly patients, because of slow wound healing.

Complications and Side Effects

Common complications and side effects of cryosurgery are listed in Table 114.9. Skin discomfort, generally a burning sensation, occurs with cryosurgery, but intensity is variable. The most sensitive areas are the fingertips, ears, and temples. Freezing of lesions on the forehead or temple may produce headaches. Treatment in hair-bearing areas can result in permanent hair

Table 114.7 Features of squamous cell carcinoma and basal cell carcinoma amenable to cryosurgery

Depth <3 mm
Diameter <2 mm
Low-risk site (e.g., trunk, extremity, cheek, forehead, neck, scalp)
Nodular or superficial basal cell carcinoma subtype (not sclerosing)
Not fixed to deeper structures
Primary lesion (not recurrent)
Well-defined margin
Well-differentiated squamous cell carcinoma

Table 114.8 Contraindications to cryosurgery

Absolute contraindications	Relative contraindications (perform with caution)
Agammaglobulinemia	Anticoagulant use
Cold intolerance	Blistering disorders
Cold urticaria	Dark-skinned person
Cryofibrinogenemia (large areas)	Infants
Cryoglobulinemia (large areas)	Older persons
Immunosuppression	Sensory loss
Impaired vascular supply	Sun-damaged or irradiated skin
Multiple myeloma	Therapy overlying a bony prominence
Pyoderma gangrenosum	
Raynaud disease (digital cryotherapy most concerning)	
Unexplained blood dyscrasia	

Table 114.9 Complications of cryosurgery

Type	Adverse effect
Immediate	Bleeding, blistering, edema, nitrogen emphysema, pain, vascular headache, vasovagal syncope
Delayed	Bleeding, excessive granulation, infection, tendon rupture, ulceration
Temporary	Altered sensation, hyperpigmentation, hypertrophic scarring, milia, pyogenic granuloma
Permanent	Alopecia, atrophy, cartilage necrosis, hypopigmentation

loss. Hypopigmentation is common, especially with longer freeze times, but is less noticeable in light-skinned patients and improves within several months. Hypopigmentation is caused by the greater sensitivity of melanocytes to freezing, a situation that can be used to advantage in the treatment of dermatofibromas, which frequently have some mild overlying hyperpigmentation. Feathering of the freeze margin (lighter freeze area) often results in a better transition of pigmentary changes. Freezing for less than 30 s beyond initial freeze ball formation does not result in scarring because of the preservation of fibroblasts and the collagen network of the dermis, which allows migration of the cellular components in the healing process and rebuilds the normal integrity of the skin layers. Although rare and usually temporary, sensory nerve damage has been reported occasionally in large case series, which may sometimes take 12–18 months to resolve.

Conclusions

If performed properly, cryosurgery is a relatively safe and simple procedure with few contraindications and low complication rate (Table 114.10). It provides good to excellent cosmesis, short duration, low cost, and high healing rate in difficult areas. It is also suitable

Table 114.10 Advantages of cryosurgery vs. conventional surgical techniques

Anesthesia optional
Excellent cosmetic results
Low cost
Low risk of infection
Minimal wound care
No need for suture removal
No work or sport restriction
Portable to multiple treatment settings
Safe procedure
Short preparation time
Useful in pregnancy

for use with no general or local anesthesia in wide population of patients including older, nonoperable, or pregnant individuals.

References

Zouboulis CC. Principles of cutaneous cryosurgery an update. Dermatology. 1999;198:111–7.

Further Reading

Andrews MD. Cryosurgery for common skin conditions. Am Fam Physician. 2004;69(10):2365–72.

Har-Shai Y, Sabo E, Rohde E, Hyams M, Assaf C, Zouboulis CC. Intralesional cryosurgery enhances the involution of recalcitrant auricular keloids: a new clinical approach supported by experimental studies. Wound Repair Regen. 2006;14:18–27.

Ismail M, Bokaee S, Davies J, Harrington KJ, Pandha H. Inhibition of the aquaporin 3 water channel increases the sensitivity of prostate cancer cells to cryotherapy. Br J Cancer. 2009;100:1889–95.

Ismail M, Morgan R, Harrington KJ, Davies J, Pandha H. Immunoregulatory effects of freeze injured whole tumor cells on human dendritic cells using an in vitro cryotherapy model. Cryobiology. 2010;61:268–74.

Sabel MS. Cryo-immunology: a review of the literature and proposed mechanisms for stimulatory versus suppressive immune responses. Cryobiology. 2009;58:1–11.

Zimmerman EE, Crawford P. Cutaneous cryosurgery. Am Fam Physician. 2012;86(12):1118–24.