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ABSTRACT

Introduction: Cryotherapy is a controlled and targeted destruction of diseased tissue by the application of low temperatures. It is a simple, cost-effective, efficacious and esthetically acceptable modality for the treatment of various dermatoses. **Indications:** It is indicated in the treatment of a wide variety of skin conditions, including benign tumors, acne, pigmented lesions, viral infections, inflammatory dermatoses, infectious disorders and various pre-malignant and malignant tumors. **Facility:** Cryosurgery is an out patient department procedure and can be undertaken in a clinic or minor procedure room. **Instrumentation and Equipment:** Several cryogens such as liquid nitrogen, nitrous oxide and carbon dioxide are available, but liquid nitrogen is the most commonly used. **Techniques:** Different techniques of application of the cryogen include the timed spot freeze technique (open spray and confined spray method), use of cryoprobe or the dipstick method. The choice of the method is based on the type of lesion. The procedure is undertaken under aseptic conditions, usually without any anesthesia. The number of freeze thaw cycles needed may vary from lesion to lesion. It is important to know the freeze time for each condition, number of sessions required and the interval between the sessions to achieve good cosmetic results with minimal complications. **Contraindications:** The treating physician should be aware of the absolute and relative contraindications of the procedure, such as cold urticaria, cryoglobulinemia, Raynaud's disease, collagen vascular diseases, etc. **Complications:** While cryosurgery is usually a safe procedure, complications may occur due to inappropriate patient selection, improper duration of freezing and freeze thaw cycles. The complications may be acute, delayed or protracted. In Indian skin, post-inflammatory pigmentary changes are important but are usually transient. **Physician qualification:** Cryotherapy may be administered by a dermatologist who has acquired adequate training during post-graduation or through recognized fellowships and workshops dedicated to cryotherapy. He should have adequate knowledge of the equipment and pre- and post-operative care. Understanding the underlying pathology of the lesion to be treated, particularly in malignant and pre-malignant lesions, is important.

Key words: Cryosurgery, Dermatosurgery

INTRODUCTION

Cryotherapy is a controlled and targeted destruction of diseased tissue by the application of cold temperature substance. It is used for the treatment of diverse benign lesions and well-circumscribed pre-malignant

and malignant tumors.

STATUS OF CRYOTHERAPY IN THE PRESENT ERA

In the present age, despite the advent of several ablative procedures like radiofrequency or laser

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LEVEL OF EVIDENCE

Level A: Strong research-based evidence; multiple relevant, high-quality scientific studies with homogeneous results.
Level B: Moderate research-based evidence; at least one relevant, high-quality study or multiple adequate studies.
Level C: Limited research-based evidence; at least one adequate scientific study.
Level D: No research-based evidence; expert panel evaluation of other information.
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therapy, cryosurgery continues to occupy a very important position in the therapeutic armamentarium of a dermatologist. It is a very safe, inexpensive, reproducible, repeatable and simple office procedure. It requires a short preparation time, is a sutureless procedure with minimal risk of infection and no anesthesia is usually required. It can be performed at any age, including in old patients with pacemakers in whom electrocautery is contraindicated, those on anticoagulants, patients allergic to anesthetic agents, patients with transmissible conditions such as human immunodeficiency virus (HIV) and hepatitis, during pregnancy and over most of the body sites. It provides high healing rates even in difficult areas, with excellent cosmetic results if performed appropriately. In view of all these advantages, it is regarded as a treatment of choice by many dermatologists for various benign and malignant dermatoses.

Theoretical background: mechanism of cryoablation

Tissue destruction occurs as a result of rapid heat transfer from the tissue causing tissue injury, vascular stasis and occlusion and inflammation.

On spraying the cryogen, there is a rapid transfer of heat from the tissue to the cryogen, with ice formation in the extracellular compartment. The extracellular solutes are concentrated, setting up an osmotic gradient, with movement of fluid extracellularly and concentration of solutes within the cell leading to cell damage. The ice crystals also damage the cell membrane mechanically. Moreover, intracellular ice formation occurs, damaging organelles like mitochondria and endoplasmic reticulum. There is severe vasoconstriction and endothelial damage due to cold temperature leading to platelet aggregation and microthrombi formation, producing ischemic necrosis of the tissue. There is inflammation in response to cell death causing further destruction.^[1-15]

There is differential sensitivity of each cell or tissue to cryodamage, with melanocytes and deeper epidermal cell layers being very sensitive and dermal collagen being cryoresistant.

Rationale and scope: The guidelines include information on the apparatus and cryogens required for cryotherapy, pre-operative preparation, various techniques to be adopted in order to achieve good cosmetic results with minimal complications, post-therapy complications that can be encountered and

their management, indications for cryotherapy, number of sessions required, interval between sessions and number of freeze thaw cycles for each type of lesion. An approach to minimize side effects and maximize efficacy is suggested. The complications and contraindications of this procedure are also addressed.

Physician qualification: A qualified dermatologist can undertake cryotherapy after receiving adequate training in the field during post-graduation or through recognized fellowships and workshops dedicated to cryotherapy. A 1-day demonstration workshop is adequate to learn this procedure.

Facility: Cryotherapy can be undertaken in a physician's office procedure room or minor theater with a high degree of aseptic precautions. A fully equipped minor operation theater with good lighting, appropriate minimal sterilization and storage facilities is desirable.

CRYOGEN

The commonly used cryogens include:^[15-17]

Cryogens	Boiling point
Liquid nitrogen (most commonly used)	-196°C
Nitrous oxide	-89°C
Solidified CO ₂ (dry ice, CO ₂ snow)	-78°C
Chlorodifluoromethane	-41°C
Dimethyl ether and propane	-24°C, -42°C

Cryosurgery equipment

1. Cryogun/cryogen spray canister: it is a portable, light weight, hand-held device with a controllable trigger to begin and end cooling.^[15-17]
2. Cryospray nozzle, cryoprobes, spray tips, neoprene or polystyrene cones.
3. Cryoprobes: they are available in various shapes and sizes and get attached to the cryogen. They are cooled by the spray of the cryogen.
4. Cryogen storage device: they are metal cylinders/containers that store gaseous cryogens as compressed gas and have an inbuilt internal pressure equalization mechanism e.g., Dewar's gas container. The cryogen is transferred to the cryogun before the procedure by a siphon or by tilting the container to pour the cryogen into the gun via a funnel. Insulated gloves must be worn while transferring the cryogen. e.g., Brymill cryogenic system.

METHODOLOGY OF CRYOSURGERY

Counseling and consent: A written informed consent is obtained from the patient after explaining the procedure, the achievable results, recurrence rate and various complications of the procedure. The consent form should mention the possibility of temporary post-inflammatory blister formation and pigmentation alterations.

History taking and examination: A detailed history of general medical condition, previous treatment received for the condition with results and whether it is a primary or recurrent lesion, is taken. History of sensitivity to cold, cold urticaria, Raynaud's phenomenon or vascular insufficiency may be recorded. Physical examination to assess the skin type of the patient, lesional characteristics such as size, margin, location, depth, biological behavior and approximation to superficial nerves and previous treatment sites should be undertaken.

Pre-operative preparation: The area to be treated is adequately exposed and cleaned thoroughly with spirit or povidone iodine. Usually, intralesional or topical anesthesia is not required. It may be used for malignant lesions because a longer freeze time required to ablate deeper malignant tissue may produce severe pain. An anxious patient is counseled and an analgesic or antianxiety drug may be administered. The surrounding normal skin may be insulated to prevent spray of surrounding areas. Sites such as the eyes, nares and ears must be protected with goggles, gauze or padding.

Treatment: Different methods of applying the cryogen to the skin lesion include:

Timed spot freeze technique: The cryogen is directly sprayed onto the lesion through an appropriate sized nozzle, which is chosen according to the size of the lesion. The nozzle is held 1 cm from the skin surface and the cryogen is sprayed in the center of the lesion until an ice ball forms that completely encompasses the lesion (confirmed by palpating between the fingers) and the desired margin is reached. For adequate treatment, the lateral spread of freeze should extend at least 2 mm beyond the margin in a benign lesion and 5 mm or more for a malignant lesion. The spraying is continued for an adequate duration (holding time) after which the lesion is allowed to thaw to complete one freeze thaw cycle. Complete thawing is suggested by the disappearance of the frozen-white surface. For larger lesions (> 2 cm

in diameter), different parts of the lesion are treated separately with overlapping margins.

Spot freeze can be carried out in two ways:

- a. **Open spray technique** – it is used for large lesions or when light superficial freeze is desired. There are two methods for open spray:
 - (i) Paint brush method – the lesion is treated by spraying from one side of the lesion and moving up and down across the lesion.
 - (ii) Spiral method – the cryogen is sprayed initially in the center of the lesion and is then moved outward in concentric circles.
- b. **Confined-spray technique** – it is preferred for round, small, discrete lesions or those close to vital structures. In this, the range of spray is limited to a discrete area by the use of neoprene or polystyrene cones.

Use of cryoprobe: An appropriate-sized cryoprobe attached to the cryogun is directly applied to the lesion before spraying the cryogen. A thin layer of vaseline or petrolatum is applied to the probe tip to allow smooth contact with the lesion. While the cooling is occurring, the lesion gets attached to the probe, which should be raised above the surrounding normal skin by few millimeters to prevent damage to the surrounding skin. Once the lesion is frozen, it is allowed to thaw. The probe should be allowed to release spontaneously from the lesion during the thawing process and must not be pulled earlier. In this technique, a longer freezing time is required as compared with the open spray technique.

This technique is preferred in vascular lesions because direct application of the cryoprobe blanches the lesion and reduces the lesional temperature thus increasing the depth of the freeze.

Dipstick method: A cotton bud is dipped into the cryogen (liquid nitrogen slush or dry ice) placed in a disposable container and then applied firmly on the lesion until a halo of ice forms around the bud. The size of the bud should be smaller than the lesion. The depth of freeze can be increased by applying pressure on the lesion. The method has the advantage of not needing a spray or probe equipment and is therefore cheap. However, repeated applications may be necessary to achieve a proper freeze thaw.

Histofreezer: It has been primarily advocated for the treatment of warts. It is a gentler treatment than liquid nitrogen because a higher temperature is achieved, it

is less expensive and is easy to store. It is a small unit containing a liquid–gas mixture of dimethyl ether and propane in an aerosol spray can. The mixture is sprayed through a narrow tube to a cotton applicator, which is applied to the wart. The mixture evaporates and freezes the wart. A temperature of -50°C is reached at the cotton tip, which freezes the wart. In a randomized trial comparing liquid nitrogen cryotherapy and histofreezer for the treatment of hand warts, patients cured of warts were 67% and 35% ($P = 0.01$) and the number of warts that resolved were 66% and 49% ($P = 0.08$) with the two modalities, respectively.^[1] The treatments were about equally effective in dorsal non-protuberant and small (< 5 mm) warts, but the overall results of liquid nitrogen were better.

It is not available in India.

Post-treatment care

The patient is explained about the immediate skin reactions that occur post-cryotherapy. There is peripheral erythema occurring immediately to 30 min after therapy, with edema setting in within a few minutes to few hours. There may be blister formation 1–3 days later followed by crusting that lasts for up to 2 weeks. The crust falls off leaving behind a mild pinkish discoloration or erythematous atrophic scar. The patient is asked to apply a mild to moderately potent topical steroid and antibiotic combination. If the blister is large, it may be punctured with a sterile needle or aspirated with its roof left in position as a natural protective film. A non-steroidal anti-inflammatory drug (NSAID) is concomitantly administered. The treated area is best left open, washed gently with soap and water and patted dry.

Indications for cryotherapy

This procedure has been used to treat a wide variety of skin conditions shown in the appendix, e.g.^[1-49]

1. Vascular lesions
2. Benign tumors
3. Acne
4. Pigmented lesions
5. Viral infections
6. Inflammatory dermatoses
7. Infectious dermatoses
8. Pre-malignant and malignant tumors

Note: Most of the evidence on the effectiveness of cryosurgery for the above indications comes from uncontrolled trials.

With the advent of several sophisticated ablative procedures like radiofrequency ablation or lasers, the

following conditions are recommended as specific indications for cryosurgery:

- Genital warts in HIV-positive patients or during pregnancy.^[2]
- Hemangiomas/vascular malformations – macular, flat-topped, superficial lesions, exophytic lesions or those with a subcutaneous component (deep or mixed hemangiomas and malformations).^[3] (Level C evidence).
- Well-defined, superficial non-melanoma skin cancers (basal and squamous cell carcinoma), especially located on the trunk. (Level A evidence).^[4]
- As combination therapy for lesions located on covered sites. E.g., plantar warts in combination with keratolytics, keloids in combination with I/L steroids.^[5,6]

In other dermatoses, it may be used as alternate therapy, especially under the following circumstances:

- In old patients with pacemakers in whom electrocautery is contraindicated
- In patients on anticoagulants
- In subjects allergic to anesthetic agents
- Patients with transmissible conditions such as HIV and hepatitis
- For genital lesions during pregnancy
- If other ablative modalities are not available

The list of dermatoses where cryotherapy has been used along with the levels of evidence are listed in the Appendix.

Complications: These are associated with inappropriate patient selection, duration of freezing and number of freeze thaw cycles undertaken.^[7,8]

Acute complications

- Local pain – more in the periungual area, temple, plantar areas, eyelids, lips, mucous membranes. Tingling and numbness, especially on the fingers.
- Edema, especially on the eyelids, lips, labia and prepuce, more in infants and the elderly.
- Cryoblisters formation.
- Syncope (vasovagal reaction) in anxious patients.
- Headache (migraine type) after the treatment of the head and neck area.

Subacute complications

- Hemorrhagic necrosis.
- Wound infection due to the use of infected cryoprobes or redipping cotton swabs into the cryogen.

- Delayed wound healing after treatment over the extremities.
- Temporary scar hypertrophy.
- Subcutaneous emphysema due to insufflation of the underlying tissue on spraying over broken skin.

Protracted complications

Common

- Hypopigmentation, especially in dark-skinned individuals, which can be minimized by freezing for <30s. Atrophic scar, which occurs when freezing time is >30 s.
- Local hypoaesthesia due to nerve damage, especially in areas where the nerves lie superficially, such as the sides of fingers, angle of jaw, post-auricular area, sides of tongue and ulnar fossa of elbow.
- Milia formation.
- Cicatricial alopecia, which can be minimized by freezing for <30 s.

Uncommon

- Cartilage damage.
- Traumatic neuroma.
- Pyogenic granuloma.
- Fibroxanthoma.

Contraindications to cryotherapy

Absolute

- Blood dyscrasias of unknown origin.
- Cold intolerance.
- Raynaud's disease.
- Cold urticaria.
- Cryoglobulinemia.
- Lesions in which tissue pathology is required.
- Lesions in areas of compromised circulation.
- Sclerosing basal cell carcinoma (BCC) or recurrent BCC or squamous cell carcinoma (SCC) located in high-risk areas like the temple or nasolabial folds.

Relative

- Keloidal tendency.
- Collagen vascular diseases.
- Dark-skinned individuals due to the high risk of developing cosmetically unacceptable protracted hypopigmentation.
- Lesions over the nasolabial fold, eyelid margins, ala nasi and hair-bearing areas (high risk of developing alopecia, especially cicatricial alopecia).
- Patients with sensory loss at lesional sites.
- Pyoderma gangrenosum.

CONCLUSION

Cryotherapy is a simple, safe and inexpensive office

procedure for the treatment of various benign, pre-malignant and well-circumscribed malignant tumors. It provides satisfactory cosmetic results with minimal complications if patient selection is proper and if it is undertaken by a trained and experienced dermatologist.

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CONSENT FORM FOR CRYOTHERAPY

I _____, give my free and full consent to Dr. _____ for the purpose of cryotherapy for _____ with/without local anaesthesia/anti-inflammatory/NSAID, the nature and consequences of which have been explained to me. I have been completely explained the technique, its results and possible side-effects such as blistering, pigmentary changes. I understand that more than one session may be needed for complete results. I understand the limitations of the procedure and also the final results. I have been provided adequate opportunity to seek information during personal consultation and also through brochures.

Signature of patient

Signature of doctor

Signature of witness

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Appendix						
List of dermatoses where cryotherapy has been used						
Lesion	Technique	Freeze time (s)	Number of freeze thaw cycles	Margin (mm)	Number of treatment sessions	Comments
Vascular lesions						
Capillary hemangioma ^[9]	Cp	5–30	1–2	1	1–4 at an interval of 8 weeks	Cryotherapy is considered to be superior to pulsed dye laser in hemangiomas with an elevated and/or subcutaneous component (Level C evidence) ^[3]
Cavernous hemangioma ^[10]	Cp	5–30	2	1	2–4 at an interval of 8 weeks	Cryosurgery performed in areas where immediate treatment is indicated, like the periorcular area, nose, lips and the anogenital area
Spider nevus ^[9]	Cp	5	1		1	
Angiokeratoma of mibellii ^[11]	Cp or os	10	1	1	3 at an interval of 8 weeks	
Angiokeratoma of fordyce ^[11]	Cp or os	10	1	1	3 at an interval of 8 weeks	
Venous lake ^[12]	Cp	10	1	1	Single	Ice ball should not extend beyond the vermilion border to prevent unsightly hypopigmentation
Cherry angioma ^[11]	Cp	10	1	< 1	Single	
Pyogenic granuloma ^[13]	Os	15	1	< 1	Single	
AIDS-related Kaposi's sarcoma ^[14]	Os	15–30	1–2	3	3 at an interval of 3 weeks	
Benign tumors; cryotherapy is a valuable alternative or adjuvant to other ablative procedures in certain situations (see Introduction)						
Milia ^[15]	Cp	Ice formation	1	1	Single	
Myxoid cyst ^[11]	Cp or os	30	2	1	1–3 at an interval of 8 weeks	
Syringoma ^[16]	Cp	Ice formation	1	1	2–3 at an interval of 4–8 weeks	
Trichoepithelioma ^[17]	Cp	Ice formation	1	1	2–3 at an interval of 4–8 weeks	

		Appendix (Contd...)	
		1	1
Trichilemmal cyst ^[17]	Os	Ice formation	2-3 at an interval of 4-8 weeks
Steatocystoma multiplex ^[18]	Os	Ice formation	2-3 at an interval of 4-8 weeks
Skin tag ^[19]	Os	5-10	Single
Dermatofibroma ^[20]	Cp or os	30	1-3 at an interval of 4-8 weeks
Seborrheic keratosis ^[21]	Os/cp/d	Flat lesions - 5 s Hyperkeratotic lesions - 30 s	Single
Sebaceous hyperplasia ^[20]	Os/cp	5-15	Single
Verrucous epidermal nevus ^[22]	Os	5	Up to 5 at an interval of 4-8 weeks
Acrokeratosis verruciformis ^[11]	Os	5	Several at an interval of 6-8 weeks
Dermatosis papulosa nigra ^[21]	Os/cp	Ice formation	Several at an interval of 6-8 weeks
Adenoma sebaceum ^[23]	Os	5-20	3-6 at an interval of 3 weeks
Rhinophyma ^[9]	Os	30	4-6 at an interval of 8 weeks
Xanthelasma ^[24]	Os	5	2-3 at an interval of 4-8 weeks
Porokeratosis ^[25]	Os	Ice formation	2 at an interval of 2 weeks
Elastosis perforans serpiginosa ^[26]	Os	10	2 at a weekly interval
Cutaneous horn ^[21]	Os	10-15	Single
Keloids ^[5]	Os/cp	15-30	5-10 at an interval of 4-8 weeks
Granuloma annulare ^[27]	Cp	10-20	Significant to complete remission reported in 51-85% of the cases. ^[5] Better results in combination with I/L steroids. Lesions < 2 years duration show better results
Necrobiosis lipoidica ^[9]	Cp	20-30	Some physicians prefer nitrous oxide because liquid nitrogen causes permanent atrophic scars
Acne ^[28] - alternate therapy to other physical modalities for lesions unresponsive to medical treatment			
Papulopustules	Os	2-5	

Appendix (Contd...)					
Acne cyst	Os/d	5-15	1	-	2-3 at an interval of 4 weeks Monthly - Useful for small, shallow pits than deep pitted scars. - For acne keloidalis – cryo + IL steroid. Moderate to good response (flattening) in 85% of the cases with early and, in particular, vascular acne keloids as compared with IL steroid. (Level A evidence). ^[29] - combination therapy with keratolytics better. - Pre-treatment pairing of excess verrucosity before cryotherapy is effective for plantar but not hand warts
Acne scars	Os, Paint brush technique for diffuse acne scars (cryoabrasion)	Face – 5 s. Back – 5-15 s	1	-	
Viral infections					
Common warts ^[6] : cryotherapy is standard therapy for warts and an alternative to other ablative modalities	Os/d	- 10 s. A 10-s sustained freeze was found to be more effective than traditional freeze (treating until there is a halo of ice around the wart) but carried significantly greater morbidity in terms of pain and blistering. ^[30] - Plantar warts – 30-60 s	1 2- plantar warts	2	1-3 at weekly interval
Genital warts/condyloma acuminata ^[31]	Os	10	1	1	1-3 - standard therapy for this condition -useful in podophyllin-resistant or podophyllin-undesirable lesions - better cure rates than TCA or podophyllin but less effective than electrodesiccation. ^[31] (Level A) -combination with podophyllin or TCA provides significantly faster clearance than single modality. (Level B evidence) ^[32] - safest treatment in pregnancy ^[2]
Molluscum contagiosum ^[6]	Os	Ice ball formation	1	-	
Pigmented lesions					
Melasma ^[11]	Os	Ice formation	1	Feathering – spraying lightly the border of the ice field to prevent sharp demarcation between post-treatment hypopigmentation and the surrounding skin and reduce contrast	At an interval of 4-6 weeks Cryotherapy may be an option especially in fair-skinned individuals

Appendix (Contd...)						
	Cp	Ice formation	1	Feathering	Single	Cryotherapy may be an option especially in fair-skinned individuals
Freckles ^[1]						
Idiopathic guttate hypomelanosis ^[11]	Os	5 s	1	1	At an interval of 4–6 weeks	Lesions gently frozen with liquid nitrogen have been shown to repigment in 6–8 weeks. ^[33,34]
Tattoo ^[35]	Os	30	2	1	At an interval of 4–6 weeks	Few reports have shown good efficacy in this condition. ^[35]
Solar lentigo ^[36]	Os/cp	5–10	1	Feathering	Single	A study showed comparable efficacy with dermabrasion but with higher rates of hypopigmentation. ^[37]
Lentigo simplex ^[11]	Os/cp	Light	1	Feathering	Single	In one RCT, cryotherapy was found to be twice as effective as CO ₂ or argon laser. (Level A evidence). ^[38]
Inflammatory conditions						
Psoriasis, lichen simplex chronicus, hypertrophic lichen planus, prurigo nodularis, chronic DLE ^[15]	Os	10–15 to 20–30	1			Mild resolution of psoriasis or lichen planus by inducing normal re-epithelization following physical destruction of lesions via reverse Koebner phenomenon. Efficacy is limited
Oral lesions^[39]						
Benign lesions – hemangioma, lymphangioma, pyogenic granuloma, mucocoele, papilloma.	Os – in most lesions Cp – deep and fluid-filled lesions					- Caution to be maintained while performing cryo over base of tongue, posterior wall of pharynx or tonsils as ventilatory impairment may occur - 20% recurrence after cryosurgery for leukoplakia
Pre-cancerous and cancerous lesions – leukoplakia, lichen planus, frictional leukokeratosis, erythroplasia, SCC						
Infections						
Cutaneous leishmaniasis, chromoblastomycosis, larva migrans ^[40,41]	Os/d	15–20	2		Three sessions at an interval of 3 weeks	- In a large series, cutaneous leishmaniasis was successfully treated with a simple protocol of cryosurgery with minor side effects. ^[40] - Cryosurgery was found to be useful for small lesions (< 15 cm ²) of chromoblastomycosis ^[41]
Pre-malignant skin lesions						
Actinic keratosis, actinic cheilitis, LSA ^[36,42]	Os/cp	20–30	1	3		
Bowen's disease ^[43]	Os/cp	20–30	2			

Appendix (Contd...)	
<p>Malignant skin lesions BCC, superficial SCC, lentigo maligna^[44-46]</p>	<p>2</p> <p>In RCT for BCC:- 1 FT cycle- 79.4% cure rate 2 FT cycle- 95.3% cure rate (Level A evidence)^[44]</p> <p>BCC – 5 mm SCC – 1 cm Lentigo maligna – 1 cm</p> <p>- Good prognosis after cryotherapy – superficial tumors, lesions on trunk - Bad prognosis – recurrent tumors, lesions without a defined margin, large lesions, tumors localized to the folds of central face, morphaeform BCC - Pre-cryo shave excision or curettage improves the results of cryosurgery - In a case series, the overall cure rate for non-melanoma skin cancer (NMSC) with cryotherapy was 97%, with very few recurrences^[47] - During the 30-year treatment period, the cure rate for NMSC was 98.6%^[48]</p>
<p>- Os - Fractional cryotherapy for tumors > 10 mm – initially, the center of the lesion is frozen and the procedure is repeated until the tumor size < 10 mm; followed by standard cryotherapy</p>	<p>30</p> <p>Os</p>
<p>Malignant melanoma^[49]</p>	<p>2</p> <p>Os</p> <p>Palliative therapy for multiple cutaneous metastases in disseminated stage</p>

Cp. cryoprobe; os, open spray technique; d, dipstick.