Dermatologic Cryosurgery

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Renata Strumia
Editors

Springer

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Preface

In dermatologic cryotherapy and cryosurgery, localized cold is used to improve some skin conditions or destroy and remove abnormal tissue. It utilizes cryogens to treat various benign non-cancerous, pre-cancerous, and cancerous lesions.

The advantages of cryosurgery include high success rates, few side effects of significance, relatively short recovery times, ease of performance, and reasonable cost. The disadvantages include frequent morbidity, lack of accurate margin of destruction control, and operator dependency.

Solid scientific grounds nowadays support the indications for cryosurgical and cryotherapeutic procedures, starting with understanding the mechanisms of action, the cellular and vascular events that occur during the processes of cooling and freezing, thawing and recovery, and ending with the statistical evidence of cure or relief.

This book is titled *Cryosurgery and Cryotherapy for Skin Diseases and Conditions* because in this way we address from the start semantic issues with the word cryotherapy, which we consider to be misused interchangeably with cryosurgery. For our purpose, the term "cryosurgery" is used to denote a primarily destructive procedure involving temperature reduction (such as for skin cancer), while "cryotherapy" is used to denote a therapeutic procedure where the tissues are taken to low temperature but are expected to survive (such as in pain reduction). A terminology compromise was accepted for those procedures where mechanisms of action where destruction and the involvement of immunity overlapped. We often respected the choice of words by the chapter authors.

An example of cryosurgery is the treatment of epithelial skin neoplasms by lowering them to temperatures that selectively destroy the cancer cells within them, while their surrounding tissue is spared lethal damage. Examples of cryotherapy include lowering skin temperature to induce anesthesia, preserving a severed finger for reattachment, or cooling a wart for a few seconds just to induce an immune response that hopefully will get rid of it.

It was 3 years ago that Mr. Grant Weston from Springer Publishers approached me after my almost yearly lecture on cutaneous cryosurgery at an Annual Meeting of the American Academy of Dermatology to suggest that I write the "definitive textbook" on the subject. That year another textbook (albeit not the definitive) on the same topic was just published, so I felt that the timing was suboptimal; the seed had been placed in nourishing ground. For the daunting task, it was tremendously gratifying to obtain the support of

luminaries like Gloria Graham, MD; Renata Strumia, MD; and Yaron Har-Shai, MD, who became my co-editors.

Gloria needs no introduction in the world of dermatology, and she is without a doubt the Doyenne of Cryosurgery, having written many articles, edited textbooks, lectured innumerable times all over the world, treated many, and mentored a large cadre of practitioners of the trade. Dr. Graham kept motivating us by example; although she struggled with health issues, she never quit pressing us to edit and her many friends in the field to contribute.

Renata was introduced to me by Grant. He suggested that I read a book on cryosurgery she had just published in Italian. Dr. Strumia wrote that book pretty much all by herself, and it was very much to my liking. I contacted her, met her at congresses, learned firsthand of her competence, and asked her to join us as editor and contributor; she did so with remarkable eagerness and efficiency.

Yaron's name I kept running into while reviewing cryosurgery on PubMed; Dr. Har-Shai is a plastic surgeon in Israel who has a keen interest in the reduction of keloids and has developed innovative techniques. He was also a most efficient deliverer of contributions to our text, and he helped us recruiting erudite authors for several chapters. I would also want to give a special thanks to Dr. Robert Schwartz for his help in the final stretch of this book. He dedicated a lot of his time and his team's effort to complete chapters for which we had difficulties finding willing contributors.

I am in great debt to my co-editors for their efforts and collaboration. They all actively participated in the development of the content, wrote a great number of the chapters, and helped me greatly in the selection of contributors of the highest quality, expertise, and recognition in their respective fields.

Finally, I must acknowledge the valuable participation and intense dedication and efforts of the team Alba Quiñones, MD (from Dermatology Treatment and Research Center) and Michael D. Sova (Developmental Editor for Springer Science) to whom this text owes its crystallization.

Hopefully the readers will find this book to be of value, as complete as possible, and enjoyable to read; it may not be the "definitive textbook" on the subject, but hopefully that is because the field continues to expand and progress.

Dallas, TX, USA William Abramovits

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Part I

History

The History of Dermatologic Cryosurgery

1

William Abramovits

Abstract

The therapeutic use of "extreme" cold dates from the mid nineteen century. For over a hundred years cryosurgery has been used to treat skin cancer; also skin infections, benign tumors, and a myriad of other conditions. Understanding of the mechanism by which cold affects the skin and other organs has led to the development of progressively better delivery systems, cryogens and monitorization equipment; all this thanks to the contributions of many bright medical and other scientific minds which we attempted to recognize in this chapter.

Keywords

History • Liquid air • Carbon dioxide • Liquid oxygen • Liquid nitrogen • Isotherms • Monitorization • Cryotherapy • Cryosurgery

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Although the history of the use of lowered temperatures for therapeutic purposes may go as far back as ancient Egypt and Greece its early use, was intended to provide analgesia and inflammation relief. Frostbite, an injury due to ice crystal formation in superficial and deep tissues was appreciated long before; a 5,000-year-old mummy found in Chilean mountains represents the earliest documentation of its occurrence [1, 2].

Dermatologic cryosurgery textbooks and scholarly reviews credit James Arnott, with the first publication on the destruction of skin tissue by means of "extreme" cold (circa 1851), which he achieved by mixing finely crushed ice and sodium chloride, recommending it in acne, neuralgia and

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to anesthetize skin preoperatively; and supposed the curability of cancers by congelation [3].

Campbell White, in articles published in 1899 and 1901 advocated the use of liquid air for the treatment of a variety of skin conditions including lupus, herpes zoster, chancroid, nevi, warts, leg varicosities, carbuncles and epitheliomata. About the latter he said that treated early it will always be cured [4].

Whitehouse, H in 1907 reported on the use of liquid air on vascular nevi, lupus erythematosus and epitheliomata; about the latter he found it to be more successful at eradicating recurrences than repeat radiotherapy; that same year Bowen, JT and Towle, HP reported on the successful use of liquid air on vascular lesions [4–6].

Hall-Edwards, J in 1911 reported on the use of carbon dioxide (CO2) in many conditions, but most notably on "rodent ulcers" [7] an old term for ulcerated basal-cell carcinomas and on the same year Cranston-Low explained the results of cryosurgery as the sum of its directly injurious, thrombotic and inflammatory effects [3–5].

Gold, J in 1910 reported on the comparison of the effects of liquid air versus CO2 stating with "no hesitancy" that the former is "far preferable" [8].

In the 1920s and 1930s liquid oxygen was used for the treatment of acne.

Irvine, H and Turnacliffe, D in 1929 favored liquid air and oxygen over CO2, reporting on the use of the former in seborrheic and senile keratosis, lichen simplex, poison ivy dermatitis and herpes zoster; and of liquid oxygen for warts, including plantar [9, 10].

Pussey, W in 1935 popularizes the use of CO2 snow derived from steel cylinders that kept it in liquid state, which when allowed to escape, turns into a fine snow that can be compressed into shapes for particular treatments; Pussey successfully treated a large black hairy nevus on a girl's face, as well as warts, nevi and lupus erythematosus. He also recognized the low scarring potential of cryosurgery [6].

Allington, HV in 1950 is the first to publish on the satisfactory use of liquid nitrogen in the treatment of warts, keratosis, superficial hemangiomas, leukoplakia, keloids, acute contact dermatitis, lichen simplex and planus, pyogenic granulomas, discoid lupus and acne. His cure rates treating common warts surpassed 90 % in three treatments done dipping cotton swabs into thermos bottles containing liquid nitrogen. Besides his elegant description of the method he used, histologic findings of post-cryosurgery were reported in the article [11].

In the 1960s several reports are made of the use of CO2 from dry ice, pulverized and wrapped into bags (golf ball size) lined with gauze, sometimes mixed with precipitated sulfur, and doused with acetone, in acne therapy.

Cooper, IS in 1963 reported on the use of liquid nitrogen to destroy or extirpate benign and malignant skin lesions; he had developed an apparatus to deliver liquid nitrogen targeted for neurosurgical use [13].

Torre, D [14] in 1965 and Zacarian, S [15] in 1967 presented hand held devices to spray liquid nitrogen that were particularly well suited to the dermatology practice; later on both dermatologists wrote extensively on the subject, particularly Zacarian who published a textbook on Cryosurgery of Skin Cancer, and Cryogenic Techniques in Dermatology in 1969 and two other in 1977 and 1985 [16–18]. Torre edited an issue of the Journal of Dermatologic Surgery and Oncology wholly dedicated to cryosurgery in 1983 [19].

Gage, AA in 1965 [20] writes on cryosurgery of the lip and oral cavity, later on benign and malignant lesions of the mouth; then on its use for pilonidal cysts, basal and squamous cell carcinoma, lentigo maligna, and on ear cancer. His body of work exceeds 70 papers listed in the PubMed database and many textbook chapters.

Gage has made major contributions to the field of cryobiology, the understanding of the mechanisms by which cryosurgery works, and to its monitorization.

Graham, GF in 1971 [21] reviews the use of cryosurgery in the treatment of malignant lesions of the skin and later publishes on the success rates of this modality for the ablation of basal cell carcinomas. Graham, GF writes and lectures extensively; in 1994 she was the Chair of the Task Force that developed the American Academy of Dermatology Guidelines of Care of Cryosurgery.

Other distinguished and contemporaneous contributors to the field of dermatologic cryosurgery include: Emmanuel Kuflik, Rodney Dawber, Gilberto Castro-Ron, Reimo Suhonen, Ronald Lubritz, Lazlo Biro, José M. Férnandez-Vozmediano, Peter Nordin, CC Zouboulis, José Carlos d'Almeida-Gonçalves and my co-editors and chapter writers for this textbook.

A PubMed review of a cross search of cryosurgery and dermatology found the following list of diseases as one time or another since 1963 when the database began to have been reported as amenable to cryosurgery treatment [12]:

Molluscum Contagiosum, Actinic Keratosis, Elastosis Perforans Serpiginosa, Basal and Squamous Cell Carcinomas, Lentigo Maligna, Lentigo Maligna Melanoma, Melanoma Maligna, Hemangiomas, Trichoepitheliomas, Porokeratosis of Mibelli, Kaposi's Sarcoma, Mucous Cyst, Hemorrhoids, Pilonidal Cysts, Nevus Flammeus, Condyloma, Cylindroma, Herpes Simplex, Telangiectasia, Atypical Fibroxanthoma, Bowen's Disease, Angiofibromas of Tuberous Sclerosis, Cherry and Capillary Angiomas, Cavernous Hemangiomas, Epidermal Nevus, Keloids, Lichen Sclerosus and Atrophicans, Erythroplasia of Queyrat, Verruciform Epidermodysplasia of Lewandowski and Lutz, Extramammary Paget's Disease, Actinic Comedonal Plaque, Prurigo Nodularis, Tattoos, Pigmented Nevi, Carbuncles, Clear Cell Acanthomas, Trichiasis, Dermatofibromas, Sebaceous Hyperplasia, Angiolymphoid Hyperplasia, Tricoepithelioma, Chalazion, Neurodermatitis, Bowenoid Papulosis, Leishmaniasis, Lupus Erythematosus, Idiopathic Guttate Hypomelanosis, Lymphocytoma Cutis, Leukoplakia, Hypertrophic Scars, Xanthogranulomas, Cutaneous Larva Migrans, Granuloma Annulare, Facial Eosinophilic Granuloma, Xanthelasma, Leiomyosarcoma, Actinic Cheilitis, Pearly Penile Papules, Venous Lakes, Granuloma Faciale, Giant Cell Tumor, Milia, Rhinophyma, Pyogenic Annulare, Chomomycosis, Epidermodysplasia Verruciformis, Verrucous Hyperplasia and Carcinoma, Acrokeratosis Verruciformis of Hopf, Seborrheic Keratosis, Merkel Cell Carcinoma, Keratocanthoma, Myasis, Multinucleate Cell Angiohistiocytoma, Blue Rubber Bleb Nevus Syndrome, Lobomycosis, PTEN Hamartoma Tumor Syndrome, Oral and Acral Pigmentation of Laugier-Hunziker Syndrome, Xeroderma Pigmentosa, and Kindler Syndrome.

The same review found the following as complications of cryosurgery: Pruritus, neuropathy, residual tumor, relapses and recurrences, loss of pigment, reactive lentiginous hyperpigmentation, delayed wound healing, hypopigmented, hypertrophic and depressed scars, retraction at the free margins of lips and eyelids, pseudoepitheliomatous hyperplasia, hyperemia, erythema, edema, bullae, loss of lashes, hairs and meibomian glands, damage to the lacrimal system, bacterial and viral transfer risk, erosive pustular dermatosis of the scalp, amelanotic melanoma at recurrence.

A progressive understanding of the mode of action of cryosurgery includes reports on cryogen induced low temperatures on animal and human skin, measurements of temperatures below the skin surface, the influence of blood flow on freezing and thawing times [13], the evaluation of circulatory events during and after cryosurgery versus before it, the histopathology of the cryo-lesion, the finding of the minimal temperature lowering leading to epidermal necrosis, the effect of cryoprotective agents, the determination of the temperatures lethal do different cells, comparative histologic observations between thermo and cryonecrosis, vascular induction of cryolesions by thrombotic events, the mediators of pain during and post-cryosurgery, the effect of anesthesia and epinephrine on cryolesions, the detection of antibodies to epidermal cytoplasmatic antigens and cell mediated immunity post procedure, induction of stress (heat shock) proteins, immunomodulatory effects of cryosurgery on melanoma response, wound healing and scarring from different freezing protocols, long-term effects of cryosurgery on cutaneous sensation, the ablative effects of freeze-thaw times and cycle repetition, the use of clobetasol [14] and antimicrobials to reduce inflammation and infections post-procedure, the differential effects of various refrigerants.

An array of methods have evolved from the times that a simple thermometer was used to read the skin temperature at the site of application of cryogens or of the cryogens themselves; monitorization has progressed from the visual and tactile estimation of frozen skin margins, and the duration of freeze and thaw times, to the use of thermocouple needles that allow for more accurate estimation of temperatures below the surface and at expected lesion depth [15, 16]. Other modalities currently being used to estimate depth and intensity of freeze and to match those to targets include: Measurements of electrical impedance [17] and current flow, ultrasound and echography to estimate tumor extent, increase the precision of thermocouple placement and detection of a match of cryodestructive isotherms and tumor extension [18], The use of magnetic resonance imaging (MRI) [19], optical coherence and impedance tomography, real time infrared guidance, second-harmonic generation microscopy and in vivo reflectance confocal microscopy.

Other ways to optimize the success of cryosurgery evolving over the years include combinations with supervoltage, curettage and radiofrequency for preoperative debulking, the use of epinephrine in the local anesthetics, retinoids orally and topically, chemotherapeutic agents, non-steroidal anti-inflammatories, immune-stimulatory agents including imiquimod and tumor necrosis factor alpha, and tagging tumor cells with metallic nanoparticles, and sclerosing agents.

The incessant understanding of the mechanisms of action of lower temperatures and of the imaging technologies lead the way to increasing success for cryotherapy and cryosurgery.

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Part II

Physics

Principles of Cryoablation

2

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Abstract

This chapter describes the development of the use of freezing temperatures in therapy. The principles of biological freezing were established in early work on frostbite and on cryopreservation protection. These led to an understanding of the tissue response to freezing, the mechanism of cryogenic injury, and the techniques of cryosurgery. Modern cryosurgery requires monitoring by temperature measurement and by diverse imaging techniques, which continue to evolve.

Keywords

Cryosurgery • Cryotherapy • Cryoablation • Adjunctive therapy • Tissue freezing • Tissue ice

Introduction

The use of low temperature to palliate pain and to manage inflammation has been exploited since the dawn of history. The written records of the Egyptian surgeon Imhotep dating back to 2600 BC describe the therapeutic use of cold [1]. The first use of freezing as a debulking and potentially curative process was extensively described by Arnott in the mid-1800s following the use of "salted ice" mixtures (~ −24 °C) to treat visible tumors of the breast and uterus [2]. Half a century later stepwise advancements in cryogenic engineering would permit access for medical use to ultracold cryogens. Key developments included the discovery of the Joule-Thomson effect in 1853, cryogen liquefaction (Caillete 1877; von Linde 1895) and Dewar's 1892 invention of the vacuum insulated thermos (dewar) essential to maintaining and handling a volume of liquefied gas.

Liquid cryogens found their earliest therapeutic use at the turn of the twentieth century when White reported on the successful treatment of

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various dermatologic conditions [3, 4]. Over the next half-century numerous cryogens were employed including liquid CO_2, N_2O, liquid air, liquid oxygen and ethers. LN was first employed in 1950 as a non-combustible cryogen to replace liquid oxygen [5]. To this point in time dermatologic applications of freezing were limited to surface treatments with cryogen sprays or topical liquid application. In 1961, Cooper and Lee [6] developed the first cryoprobe that could be inserted through the skin for treatment of bulky skin lesions and or visceral tumors. With this development dermatologists had access to a multiplicity of cryosurgical tools supportive of relatively precise tumor treatment.

Principles of Biological Freezing

With the growing interest in diverse cryoablative strategies, a need to understand underlying principles of freezing and its consequential mechanisms of action in tissue became apparent. Numerous studies of the damaging effects related to frostbite along with a developing understanding of cellular freeze protection during cryopreservation procedures established a base line of relevant knowledge.

The application of a cryogen in various forms (i.e. metallic probe, fibrous wick, surface spray, etc.) to a targeted tissue, once "activated," acts as a heat sink to remove thermal (heat) energy. As tissue cooling progresses, water molecules slow, tend to aggregate into a structured lattice and form an ice crystal. Ice growth proceeds outwardly from the "cryoprobe" by accretion of water ahead of the freeze front at a rate dependent on the heat extraction capabilities of the cryogen. The rate of freezing is always more rapid proximal to the "cryoprobe." Hence, the rate of freezing varies over the radius of the freeze zone resulting in less damaging effects in the periphery of the frozen tissue mass. This discontinuity may yield cell survival within the distal regions of the tissue target or in those cells near active vasculature. For this reason, a second freeze following the first thaw is common practice since a second "partially lethal" freeze yields an additive destructive outcome. The second freeze, while use has been historically empirical, gains significance as it is now recognized that indolent cancer cells and cancer stem cells are far more resistant to varied therapeutic assaults and are no doubt the foci of cancer recurrence [7].

Tissue Response to Freezing

Depending upon the severity of the freezing during a cryosurgical procedure, the tissue's responses to cold injury may range from reversible inflammation to cellular destruction. This difference is the basis for a selective therapeutic response. Short duration freezing at elevated subzero temperatures produces only a mild inflammatory response with limited therapeutic uses such as the treatment of retinal detachment. Severe freezing produces destruction of cells through two processes: (1) physical effects of cell rupture due to osmotic shock and intracellular ice formation and (2) activation of stress signaling cascades that launch numerous molecular mechanisms of cell death (i.e. apoptosis, autophagy and necrosis). Some differences in the sensitivity of diverse cell types to cold injury and even freezing have been reported which may be exploited for therapeutic purpose [8].

The cryogenic lesion is characterized by a central portion of coagulation necrosis, which collectively consists of death via physical trauma, rapid-onset apoptosis, and necrotic populations. With a relatively thin peripheral zone or freeze margin cell destruction is uncertain. Shortly after thawing, the tissue appears hyperemic within the border region of the previously frozen volume with an edematous central zone. Maximal levels of apoptosis are evident within the core within 1–2 h following thawing, whereas elevated levels are seen in the periphery several hours later while necrosis is observed immediately post-thaw (primary necrosis) and in the following days (secondary necrosis). The border of the previously frozen tissue may be critical to therapeutic management. In this region tissue temperatures ranged from 0 to −20 °C, yielding some live cells, some dead, and others partially damaged

hovering between life and death [9, 10]. It is within this region that high numbers of delayed apoptotic and secondary necrotic cells are evident. Hence, the therapeutic challenge is to ensure the death of all cells in this region. While a challenge, the involvement of molecular mechanisms of cell death offers the potential for combination strategies to enhance death [7].

The injured tissue begins the repair process quickly with the infiltration of inflammatory cells migrating through the necrotic tissue. Over the following weeks to months, a fibrous, pliable collagen scar laid down by fibroblasts slowly replaces the necrotic tissue The preservation of the collagenous matrix helps retain the tissue architecture which facilitates tissue repair, and healing.

Mechanisms of Cryogenic Injury

The mechanism of tissue injury from freezing is complex as the numerous consequences of a freeze-thaw cycle have a global impact on cellular homeostasis. Direct injury to the cells caused by ice crystal formation might also include microcirculatory failure. The cascade is completed with the post-thaw induction of apoptosis and cellular necrosis. Extracellular ice crystal formation, especially in the peripheral region of the freeze zone, removes water from the cells causing major deleterious metabolic disequilibria related to solute concentration, the "solution effects". Ice crystals also cause mechanical damage due to cell membrane disruption, intracellular ice crystal formation and shearing forces, especially in highly organized tissues. The vascular stasis that follows thawing constitutes a major mechanism of injury within the volume of previously frozen tissue thereby increasing the probability that cells die. While the relative importance of these two mechanisms of injury has long been debated, the two are clearly synergistic in cryoinjury leading to cell death from freezing [11–14].

Apoptosis or programmed cell death has been identified as a mechanism of cell death associated with thermal injury [15]. In investigations with human prostate cancer cells in vitro, Hollister et al. described cells dying from apoptosis some days after freezing [16, 17]. Experiments in vitro have shown that apoptosis occurs following exposure to modest freezing temperatures and that cells are susceptible to apoptotic initiation events up to 12–24 h after thawing [18–21]. Clarke et al. observed cell rupture and necrosis immediately post-thaw, while apoptotic cell death was prominent 12-h post-freeze [19]. Subsequent studies, apoptotic death showed this to be partially regulated through the mitochondria [21–23]. The mitochondria play an important role in the apoptotic death cascade, most notably through the influence of the Bcl-2 family of proteins, regulators of apoptosis [23–28]. More recently, Robilotto et al. identified a temporal wave of apoptosis induction initiating within an hour post-thaw at the core of the frozen mass when ultra-low temperatures are attained followed by the movement of apoptotic induction outward towards the periphery over the next 18–24 h [22]. Further, this study revealed that the rapid induction of apoptosis at ultra-low temperatures progressed through a membrane-mediated pathway whereas the delayed apoptosis in the periphery progressed through a mitochondrial-mediated pathway.

The Freeze-Thaw Cycle

Cryosurgical technique requires that tissue be rapidly frozen, thawed slowly and completely, and then exposed to a second freeze cycle so that the goal of achieving a temperature in the targeted tissue is attained along with a safe margin around the tumor [12, 14, 29]. Each of the multiple phases of the freeze-thaw cycle (i.e. cooling rate, tissue temperature, freezing duration, and thawing rate contribute to tissue injury) are highly damaging to cells. Repetition of the freeze-thaw cycle subjects the tissues to a repeat injurious paradigm important to complete tumor destruction. The characteristics of each of these phases of the cycle vary in relation to the distance from the cryosurgical probe. This cycle of freezing also allows for the driving of ablative isotherms (−20 °C or −40 °C) further out from the cryoprobe region helping increase the level of cell destruction [30].

Rate of Tissue Cooling

Rapid cooling increases the probability of lethal intracellular ice crystal formation. Intracellular ice formation typically occurs at cooling rates greater than 20 °C per minute [29, 31]. In clinical practice, the cryosurgical probe should always be used at the lowest attainable temperature to obtain a greater probability of intracellular ice formation since much of the frozen tissue volume will be subjected to only slow cooling rates. Additionally, studies have shown that the rapid induction of membrane mediated apoptosis at ultra-cold temperatures and rapid-cooling rates starts the cancer cell down an irreversible path to death therefore increasing the possibility of cancer destruction [22].

Target Tissue Temperature

Tissue temperature is the critical factor in the application of a cryosurgical technique. Cell death occurs in greater numbers as the tissue temperature is lowered toward a nadir. Cells from different tissue sources demonstrate different lethality ranges [8, 16, 32]. Those of dermatologic origin are typically the most sensitive to freezing while those of the prostate are far hardier. Most skin lesions are fully ablated at temperatures between −10 and −20 °C while certain prostate cancers require a range between −40 and −80 °C. Studies have also demonstrated that the molecular disposition of a specific cancer type can also influence the cells response to freezing. For instance, Klossner et al. demonstrated that early stage androgen responsive prostate cancer is more resistive to freezing injury than the late stage androgen non-responsive prostate cancer cells [32].

Duration of the Freeze-Thaw Cycle

Studies that would definitively establish the duration of freeze cycle (i.e. duration of nadir temperature holds during a single or double freeze and interval between first and second freeze cycle) are wanting. While longer durations are intuitively beneficial, only limited in vitro research [30, 33] provides quantitative data supporting physician practice. Hence, anecdotal evidence and physician instinct guide timing in regard to clinical practice. Hold times of a "few minutes" at the nadir temperature is thought to be adequate to assure that the targeted lesion is fully involved at the nadir and that local circulation is arrested. To this end, Klossner et al. demonstrated that hold times of 1–2 min at target temperature were adequate to result in cell death [30]. Holds of shorter duration resulted in less effective cell death where holds longer than 2 min at a given temperature did not increase the level of death. When a dual freeze-thaw cycle is applied, the thaw interval should be of adequate duration to assure passive thawing of the outer margin of the freeze zone. Passive thawing allows for prolonged exposure to the nadir temperature, which is elevated in comparison with the inner mass of the freeze zone. The repeat freeze cycle provides a double stress event to the cell population as well as allows for critical temperatures to be driven further from the cryoprobe thereby increasing the overall kill zone.

Thermocouple Monitoring

The use of thermocouples to monitor tissue temperature during freezing has emerged as an important adjunct to the imaging techniques. Needle-mounted thermocouples have proven accurate and useful for thermal monitoring, especially when inserted in critical areas [34]. Their use allows for the confirmation that lethal temperatures have been achieved in the target tissue or that injurious temperatures have not been reached in critical areas, such as in the wall of the rectum. It is important to note that thermocouples measure point sources of temperature within the tissue. As such, these temperatures cannot be extrapolated easily to the entire volume of the cryosurgical lesion.

Adjuncts to Cryoablation

Cytotoxic drugs when used as adjunctive agents offer a promising approach to increase the kill efficacy of cryotherapy along the margin of the ice ball [19–21, 23, 28]. Sub-toxic exposure to

agents such as 5-Flurouracil or Taxotere prior to the freezing insult can increase the lethal affect of freezing at the elevated sub-freezing temperatures found within the freeze zone periphery [19, 28]. The combined benefit of 5-FU and freezing is to increase the rate of apoptosis in the targeted tissue margin [19, 28, 35]. Other studies have shown that other agents such as Taxotere [23], cisplatin [16], vitamin D_3 [36, 37], TNF [38, 39], and TRAIL [40], among others, providing a synergistic benefit when used in conjunction with cryoablation raising the lethal temperature necessary from the −20 °C to −30 °C range to around −10 °C or warmer. These adjunctive strategies have shown promise to significantly improve tumor ablation.

Cryoablative Technologies

Beginning in the mid-1960s, cryoablation underwent a significant technical advancement [6] and now serves as an effective treatment modality for a number of cancers. Further technical modifications were realized in the 1990s including the development of new cryosurgical apparatus, imaging techniques, and adjunctive devices to improve the applicability and efficacy of cryotherapy. Technical improvements, such as the use of new multi-probe devices and the development and utilization of a protective urethral warming catheter may be cited as significant milestones in the evolution of cryosurgical technique [41–47]. Better selection of patients, with appropriate staging of disease, has substantially improved overall results.

Cryogen selection provides option to support diverse treatment of diverse clinical indication ranging from de-bulking to total ablation. Carbon dioxide, a cryogen with the most limiting ablative action (−78.5 °C), and nitrous oxide (−88.5 °C) find limited use. Argon (−185.8 °C) and liquid nitrogen (−195.8 °C) are more widely adopted in cryosurgical devices that operate with closed-end cryoprobes. LN is a conveniently managed liquid utilized in spray, wick and probe configurations. Recently, a next generation class of devices has been developed utilizing critical and supercritical cryogens, poised to provide far more rapid and effective freezing tissue thereby increasing the level of death while reducing the time and collateral damage associated with the freeze thaw process [48].

Modern Cryosurgery

The application of cryosurgery often relies on guidance from information derived from the imaging techniques. Ultrasound, allows for monitoring of ice ball growth progression, but has significant limitations because the practitioner cannot see beyond the nearest ice plane of frozen tissue. The resulting image is two-dimensional because acoustic shadowing precludes visualizations of the extent of freezing behind the ice front [45]. Three-dimensional ultrasound may well alleviate this problem [46, 47, 49, 50]. Another limitation of ultrasound occurs because the image provides no information about target tissue temperature, which causes difficulty in making real-time determination of where the critical −40 °C isotherm is within the ice ball. To address the issue of thermal monitoring, the use of thermocouples, in conjunction with ultrasound, has added an increased level of certainty of the success.

New directions in imaging for cryosurgery include computerized tomography (CT), magnetic resonance imaging (MRI), and electrical impedance tomography (EIT). CT has the benefit of showing the entire cross sectional image of the frozen tissue. The images are made at intervals of a minute or two, which is not real time but still within the realm of usefulness [51]. MRI provides a three dimensional view of the volume of frozen tissue and has shown promise as a clinically valuable monitoring technique in cryosurgery [52–55]. MRI data allow the temperature within the frozen volume to be established using mathematical models [56–59]. The techniques and tools for use with MRI are still evolving, as are the MRI contrast agents [60]. Harada et al. recently demonstrated the usefulness and safety of MRI-guided cryosurgery for renal tumors [61]. The probability of extensive or routine clinical use of MRI-guided cryosurgery in the near future is remote because of expense. Electrical