CHAPTER 1

General Information

INTRODUCTION TO OTHER COMPETITIVE LOCAL ADJUVANT AND ABLATION TECHNIQUE

Definition and principle

The purpose of any local adjuvant is to rapidly destroy many cells, effectively controlling tumor progression and potentially reducing or definitively eliminating the tumor.

Ablation therapy is a local treatment method for solid tumors that destroys tumor tissue through physical, chemical, or biological means.

In cases of localized lesions, cryotherapy can be used for cryoablation of the mass, either on its own or in association with subsequent surgical excision. In this scenario, cryoablation is considered a reliable and effective therapeutic approach for both benign and malignant lesions.

Despite its promising results, several alternatives have been used and described in the literature. The most used local adjuvants for orthopedic surgery include physical ablation such as radiofrequency ablation, microwave ablation, cryoablation, and laser ablation;[1-4] high-intensity focused ultrasound; irreversible electroporation;[5-8] and chemical ablation, commonly using alcoholic compounds (ethanol, phenol, etc.).

Radiofrequency ablation

Radiofrequency ablation is among the most frequently used forms of thermal ablation[9] and can be performed with percutaneous puncture, laparotomy, or laparoscopy. Needle electrodes, placed inside the target lesion, increase the local temperature to 60-80 °C or higher. The electric current in the radiofrequency range (4-500 Hz) causes ion oscillation and friction within tumor tissue, resistive heating, protein denaturation, cell death, coagulative necrosis, and tissue damage.

This method is considered efficient for lesions that are ≤3 cm, while its efficiency decreases as the tumor size increases. According to the literature, radiofrequency ablation is particularly effective for painful bone and soft tissue metastases as well as for liver cancer treatment (it is suggested as an alternative for patients not suitable for surgery).[9]

However, surgeons should always consider that heat transmission is not limited to the target tissue. Thereby, energy could dissipate into the surrounding tissues and compromise them and the lesion.3 Several studies have reported low recurrence and mortality rates, and the curative effects are similar to surgery. Patients have only reported mild adverse reactions (fever, neutrophils, local pain, and minor thermal damage in peripheral organs).[10-16]

Microwave ablation

Microwave ablation creates heat by exciting, aligning, and realigning water molecules following the variation of the electromagnetic field. Microwave energy is transmitted quickly to the target lesion through an antenna, rapidly increasing the temperature inside the lesion. Increasing the kinetic energy of the system, the tissue temperature rises to 150 °C, leading to severe damage of the target areas. Antennas of various designs can be used to deliver microwave signals.

The technique avoids electrode pads, and it is also suitable for patients with pacemakers.[17-19] This procedure is particularly indicated for large or complex solid tumors (liver, lung, kidney, spleen, breast, adrenal gland, and thyroid).[20-27] In a previous study, the authors observed major complications in 3.65% of patients and mild complications in 8.03% of patients, with no mortality.[28] In large hepatic lesions, Medhat *et al*.[29] reported 73% complete tumor ablation and no major complications or death.

Although effective, microwave power can cause side effects on other tissues, such as abscesses in solid organs, perforation of hollow organs, and hemorrhages.[30]

Laser therapy

Laser therapy works by refracting laser light on the tumor mass, where protons are absorbed and heat is produced, leading to coagulative necrosis. The technique consists of image-guided percutaneous insertion of probes into the center of the neoplasm and requires constantly measuring the temperature at the periphery of the tumor.

Laser energy is delivered until the temperature reaches 60 °C or more, at which points tissues are inevitably subjected to alterations and damage.[3, 31] The procedure has several advantages: minimal trauma, rapid clinical recovery, and precise targeting. It is mainly used for skin, liver, and prostate cancers.

High-intensity focused ultrasound

This technique focuses ultrasound beams on the tumor. The temperature rises quickly. The high temperature reached (55-100°C) causes coagulative necrosis, which disrupts tumor cells and structures.[32] Its noninvasive nature, accuracy, and minimal side effects make it suitable for several cancers in challenging body sites (uterine, liver, pancreas, and prostate).[33]

IRREVERSIBLE ELECTROPORATION

A high-voltage electric field is used to induce nanopores in cell membranes, altering cellular homeostasis, increasing permeability to chemotherapeutic drugs, and finally causing cell death. The procedure takes place without an excessive temperature increase and is therefore particularly suitable when the tumor is close to sensitive anatomical structures (major vessels and nerves). The procedure is minimally invasive, precise, and has limited collateral damage or side effects, preserving healthy tissues.[34-36]

Alcoholic adjuvants

Alcoholic adjuvants can be used with percutaneous or open injections of pure alcohol into the target tissue. Alcohols draw water from cells, inducing severe dehydration and, consequently, cell destruction. This adjuvant approach can be used alone or in association with one of those listed above. Depending on the tumor size, multiple administrations may be needed.[37, 38]

Phenol

Solutions of this aromatic organic compound have been largely used in orthopedic oncology, particularly for giant cell tumors of the bone. Administered locally, phenol induces immediate necrosis and/or apoptosis. Phenol can be suitable for treating small scattered cellular debris following intralesional curettage, whereas it is unsuitable for treating intact tumor masses.[39]

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THE HISTORY OF THERAPEUTIC HYPOTERMIA

From the dawn of civilization to the threshold of the industrial revolution

The use of low temperatures to improve people's health and to treat local or systemic diseases finds its roots in the dawn of civilization. The Egyptians used cold to treat inflammation and injuries as early as 2500 BCE. In particular, there is evidence of its use in the *Smith Papyrus*, named after Edwin Smith, who bought it in 1862. Dated to the second intermediate period of ancient Egypt, it is considered to be the oldest existing surgical treatise on trauma. It emphasizes cold's importance in treating inflammation after trauma and injury. In particular, the use of cold compresses is documented to treat fractures of the skull and other battle wounds.[1, 2]

In ancient Greece, between the 5th and 4th centuries, Hippocrates reported further use of cold materials. Although Hippocrates pointed out the dangers of prolonged exposure to low temperatures, such as convulsions or gangrene, he also recognized the therapeutic potential of cooling elements. He prescribed ice and snow to treat swelling and pain or to reduce local bleeding. He also suggested that his patients drink cold water to bring down fever.[1, 3] Hippocrates' ideas significantly influenced his contemporaries and later Roman medicine. The Roman physician Galen is credited with inventing a cold cream made of cold water, olive oil, and beeswax. He prescribed it for cooling purposes, particularly to treat fever.[4]

Although medical research stagnated during the Middle Ages, there were also advances in the therapeutic use of cold temperatures during this period. A book dated 1050 AD reported that British monks used cold as a local anesthetic for the first time in Western history.

The anesthetic effect of cold was later rediscovered during the Napoleonic era. During the historic retreat from Moscow, Napoleon's legendary surgeon Dominique-Jean Larrey recorded that amputations could be carried out painlessly if the affected limb had been sufficiently cooled in the snow before the operation. Later, in the mid-19th century, the British Dr. Richardson took a cue from Larrey's observation and extended it by introducing the ether spray, a local anesthetic agent for treating acute traumas and local pain. The compounds that have results from its evolution, which rely on ethyl chloride, are still commonly used today.[5]

The industrial era and the contribution of James Arnott

The start of the Industrial Revolution in the 19th century led to a series of technological innovations that progressively made refrigeration more efficient and less expensive. In parallel, the flourishing of medical and surgical scientific councils, alongside the birth of the first specialized journals, encouraged the spread of experiences and ideas in the medical landscape.

The English physician James Arnott (1797-1883) played a pivotal role in the birth of cryotherapy as we know it today. He published several papers on the use of cold in medicine between 1819 and 1879. Arnott took inspiration from his brother, a scientist who had already found his fame and fortune by inventing the slow-combustion stove. Arnott understood the beneficial potential of cold temperatures and was the first to orientate its activity toward it constitutively. He was the first in modern medicine to apply extreme cold locally to provoke tissue destruction and, in this regard, designed specific instruments for producing and applying temperatures down to -24 °C. He stated that a very low temperature would arrest inflammation and reduce hypervascularization.[6-8]

To achieve a temperature below 0 °C, Arnott used a mixture of salt and crushed ice ("two parts finely pounded ice and one part of chloride of sodium"). His equipment consisted of a waterproof cushion applied to the skin, two long flexible tubes to convey water to and from the affected part, a reservoir for the ice/water mixture, and a sump. This kit was exhibited at the Great Exhibition of London in 1851 and earned Arnott a prize medal.[8] Although Arnott's device was at times cumbersome to use and its freezing capacity cannot compare with modern versions, it could be used successfully to treat several pathologies. Acne, neuralgia, and headaches were all seen as suitable fields for the nascent but developing cryotherapy. It was not long before Arnott identified cancer lesions as appropriate targets for his new invention. In particular, the main therapeutic aim was the palliation of advanced accessible tumors, such as the ones that originated from the breast, uterine cervix, or skin. Freezing was used mainly to reduce pain and the tendency for local hemorrhage, but also to reduce tumor size. Arnott hypothesized that congelation could arrest the inflammation accompanying neoplasm and eliminate the vitality of cancer cells. Although palliation was his main therapeutic aim, he recognized the unfulfilled potential of cold to cure cancer, suggesting that congelation could one day be used not only to prolong the patients' life and ease their pain, but also to provide a definitive cure.[9]

From Arnott to Irving S. Cooper and modern cryotherapy

Arnott's ideas paved the way to cryotherapy as we know it today. In the decades that followed, low-temperature treatments slowly but continuously advanced alongside the progression of technology and global medical knowledge. Between the late 19th and early 20th centuries, scientists from Europe and North America developed different and increasingly sophisticated cooling systems. Leaving out those studies that used cryotherapy to treat external lesions, the Philadelphian neurosurgeon Temple Fay made an essential contribution to cryotherapy for oncological aims. Between 1936 and 1940, Fay implanted metal capsules inside the cranium of patients with inoperable brain cancers. These capsules were then connected to an external cold irrigation system to freeze the lesions, to reduce tumor size, and to relieve pain.[9, 10]

Despite the work of these pioneers, the times were not yet ripe for large-scale use of cryotherapy. After the Second World War, the literature regarding the effects of tissue freezing flourished – with a myriad of *in-vitro* and animal studies – also due to the increasing attention to other subjects such as cryopreservation. In the same years, further technological developments led to better and cheaper freezing methodologies. However, it was not before the 1960s that these two conditions converged, giving way to modern cryosurgery. Today, it is believed that modern cryosurgery began through the collaborative work of a physician, Irving Cooper, and an engineer, Arnold Lee. The duo built an innovative and automated cryosurgical apparatus cooled by liquid nitrogen. This cryosurgical probe would later become the prototype from which every subsequent liquid nitrogen cryosurgical probe was built. Made of three long concentric tubes, the probe was supplied with liquid nitrogen from a pressurized source. The inner tube served as a conduit for liquid nitrogen flow to the tip of the probe, while the space between the inner and the middle tubes provided a path for the return of gaseous nitrogen from the tip of the probe. The space between the outer tube and the middle tube was vacuum insulated and had a radiative shield, allowing the liquid nitrogen to be conducted without heat loss to the probe's tip. When applied to the tumor, such a probe allowed a rapid and continuous supply of low temperatures, resulting in *in-situ* freezing. Cooper's contribution was not limited to technical inventions; he also contributed significantly to the theoretical and clinical points of view. Cooper was the first to state that a tissue temperature of -20 °C, held for 1 minute, was sufficient to induce necrosis. Furthermore, he had a role in establishing the basic features of cryosurgical techniques such as rapid freezing, slow thawing, and repetition of the freeze-thaw cycle. Since then, the nature of cryosurgical injury has been subjected to intense investigation to define the appropriate temperature-time dosimetry and the correct number of freeze-thaw cycles in cryosurgery.[11-17]

Cooper's work has led to the broader use of cryotherapy in different branches of oncological surgery. Liquid nitrogen was the most popular cryogen from the early 1950s until the end of the 20th century due to the low temperatures achievable (-197 °C), making it suitable for benign and malignant lesions.[9] Since the beginning of the 21st century, however, nitrogen cooling devices have been progressively replaced with argon-helium cooling devices. Argon-mediated cooling takes advantage of the Joule-Thomson phenomenon and (unlike nitrogen cooling) does not provide for any change of state of the cryogen substance and does not induce the formation of physical barriers between the cryogen and the probe. Argon allows even better stability of the cooling temperatures and permits an active and quicker thaw by introducing helium gas at the temperature of 35 °C. Furthermore, argon cooling devices can be equipped with probes with smaller sizes and diameters compared with nitrogen cooling ones. This translates into better intraoperative maneuverability and accuracy.[18, 19]

Today, cryosurgery represents a reliable option for selected patients with neoplastic diseases of the skin, lung, breast, genital systems, kidney, liver, and – among others – the musculoskeletal system.

CRYOTHERAPY'S FIELDS OF APPLICATION

Apart from its uses in orthopedic oncology, which will be discussed in detail in the following chapters, cryotherapy can be used in several branches of oncological medicine and surgery. Below is a short list of the main non-musculoskeletal oncological fields of interest for modern cryosurgery.

Skin tumors

Skin cancers have long been the primary target of cryosurgery due to their superficial location, easy accessibility, and limited depth. Small skin lesions can be easily managed by cryotherapy, using liquid nitrogen nebulized as a spray from a handheld device or fitted within a metal probe placed over the tumor. Although surgical removal still represents the treatment of choice, cryotherapy has been used successfully as an alternative to surgery or, primarily, as an adjuvant treatment after curettage. This last combination, in particular, has an extremely high cure rate of >99% of benign and malignant neoplasms.[20, 21]

Kidney tumors

Surgical resection represents the gold standard for eradicating kidney cancers, regardless of size and position. However, small tumors in selected patients have been treated by image-guided cryoablation *via* percutaneous or laparoscopic techniques. This strategy can be suitable for small tumors (<4 cm), especially if located in positions such as the posterior surface of the kidney, which are tough to reach with both open and laparoscopic surgical approaches. Researchers have compared cryoablation with radiofrequency ablation, revealing comparable outcomes in terms of oncological results and complication rates.[22-25]

Liver tumors

Liver cancer was one of the first abdominal organ targets of modern cryotherapy. Liver cryosurgery is generally performed using a percutaneous approach under ultrasound guidance. This technique produces solid oncological results and acceptable complication risks. Cryotherapy and radiofrequency (one of the main competitors in this field) have comparable survival rates.[26, 27]

Tumors of the oral cavity a nd digestive tract

In the oral cavity, cryosurgery is used for various benign diseases, leading to good clinical results. However, excision and irradiation are still the preferred treatments. Going down the digestive tract, cryosurgery has also been used for the esophagus. Cryosurgical techniques that deliver a cold cryogenic spray *via* endoscopy have been used relatively widely for dysplastic mucosal disease and early-stage tumors. This approach is beneficial in around 70% of patients treated.[28-30]

Breast tumors

For decades, the use of cryotherapy has been described mainly in the treatment of locally advanced and/or disseminated breast carcinomas. Applying very low temperatures, either with a cryoprobe or spray, provides pain relief and bulk reduction and slightly prolongs the overall survival of inoperable patients. Recently, there has also been interest in using cryotherapy to treat small early-stage breast tumors *via* image-guided percutaneous approaches. The results have been encouraging in terms of safety and effectiveness, especially when associated with surgical resection.[30-32]

Prostate tumors

Modern medicine offers several therapeutic approaches for prostate carcinoma. Despite the prominent role of radical prostatectomy, which has never been disputed, there have been extensive trials involving cryosurgical treatment. Moreover, it has been recognized as an acceptable alternative to radical excision. In particular, cryotherapy has shown success for local ablation of focal lesions to allow a nerve-sparing treatment. This technique is generally seen as a compromise between early radical treatment methods, such as prostatectomy and radiotherapy, or a conservative "wait-and-see" approach. This treatment has two main theoretical limitations. The first is represented by the small size of the target lesions, implying the need for extreme precision while placing the probes. This problem can be minimized by performing the procedure under the guidance of ultrasound or another imaging modality. The second is due to the fact that, despite the increasing efforts in screening and the development of imaging instruments, only a small percentage of prostate tumors are sufficiently localized at the moment of their diagnosis to be considered for focal therapy. This seriously limits the percentage of cases that can be treated adequately with cryosurgery.[33-37]

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