THE CRYOSURGICAL TREATMENT OF BENIGN AND LOW-GRADE MALIGNANT BONE TUMORS

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THE CRYOSURGICAL TREATMENT OF BENIGN AND LOW-GRADE MALIGNANT BONE TUMORS

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

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HENDRIK WILLEM BARTHO SCHREUDER

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"THE ART OF CRYOSURGERY"

Cryosurgery is an art as well as a science.
Of course just as a sculptor or painter mus t learn about stone, wood, canvas, paper , chisels, rasps, paintbrushes, and othe r materials, the cryosurgeon must understan d the science underlying cryosurgery.
He or she must learn the properties of th e various cryogens, the apparatus for applyin g them, the three-dimensional extent of th e lesion to be treated, and the tissue content o f these lesions. He or she should also know th e susceptibility of various portions of the targe t lesion and surrounding tissues of varyin g insults with cold.

Douglas Torre, MD; Cutis 1994; 54: 354.

TO MY PARENTS

FOR JOLANTA, MAARTEN AND ANNIEK

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION AND AIMS OF THE STUDY

INTRODUCTION

The benefit of the use of cold for medical purposes has been known for a long time. The first application was a symptomatic form of treatment for all kinds of medical conditions utilizing mainly its anaesthetizing properties.
Later, when the technical knowledge became available to produce very low temperatures (less than minus 100°C) its potential power to induce cell death was discovered. Destroying diseased tissue like benign and malignant neoplasms using extreme low temperatures is now known as *cryosurgery* and is generally accepted as a therapy of value in several medical specialties. Dermatologists have been using it for over a century to treat all kind of skin disorders[1,2], and further on, for example in surgery for the treatment of liver metastases[3], prostate cancer[4] and neurological tumors[5].
In 1968 Ralph C. Marcove introduced cryosurgery in orthopaedic oncology for the treatment of primary and metastatic bone tumors by repetitive freezing and he was awarded the first price in scientific research at the 162nd annual convention of the medical society of the state of New York[6]. Since than only a few orthopaedic surgeons dealing with skeletal tumors have adopted the technique and the clinical results and experimental data of cryosurgery with specific reference to the skeletal system have been published in about 50 papers. Larger series of patients, especially "non-Marcove", are with only an occasional exception not available, but are required to confirm the benefits of the cryosurgical technique.

Cryosurgery is used as adjuvant treatment after intralesional resection (curettage) of active and aggressive benign and low-grade malignant, stage IA skeletal tumors.[7] By spraying liquid nitrogen into the curetted lesion the surgical margin of resection is extended. Tumor cells left behind are destroyed by this thermal injury, which otherwise could be responsible for a recurrence of the tumor. By this method the procedure can be considered to be marginal from the point of view of orthopaedic oncologic principles[7]. The advantage of this kind of treatment, as compared with local (en block) resection, is that as much of the supportive function of bone is preserved and that reconstructive surgery can be limited.

Since the early nineteen seventies, cryosurgery for orthopaedic oncologic indications has been used in the University Hospital in Groningen and since 1991 in the University Hospital in Nijmegen, The Netherlands.

AIMS

The aims of this thesis are defined as follows:

1 Description of *effective* cryosurgery by investigation, comprehensive recording and distillation of all in the literature available historical, technical and biological data of cryosurgery for orthopaedic oncologic purposes.
2 A literature *review* of all experimental data and clinical results of cryosurgery of bone and bone tumors.
3 Investigation of the *clinical* results, functional outcome and complications of cryosurgery as adjuvant therapy for benign and low-grade malignant bone tumors.
4 Development and evaluation of equipment for local and general *monitoring* of the cryosurgical process.

REFERENCES

1 **Graham GF and Hill C.** Advances in cryosurgery during the past decade. Cutis 1993; 52: 365-72.
2 **Kuflik EG.** Cryosurgery updated. J Am Acad Dermatol 1994; 31: 925-44.
3 **Onik GM, Atkinson D, Zemel R and Weaver ML.** Cryosurgery of liver cancer. Sem Surg Oncol 1993; 9: 309-17.
4 **Zippe CD.** Cryosurgical ablation for prostate cancer: a current review. Sem Urology 1995; 13: 148-56.
5 **Maroon JC, Onik G, Quigley MR, Bailes JE, Wilberger JE and Kennerdell JS** Cryosurgery re-visited for the removal and destruction of brain, spinal and orbital tumours. Neurol Res 1992; 14: 294-302.
6 **Marcove RC and Miller TR and Cahan WC.** Treatment of primary and metastatic bone tumors by repetitive freezing. Bull N Y Acad Med 1968, 44: 532-44.
7 **Enneking WF.** A staging system of staging Musculoskeletal Neoplasms. Clin Orthop 1986; 204: 9-24.

CHAPTER 2

THE MEDICAL USE OF LOW TEMPERATURES

The use of low temperatures has become an essential, sometimes indispensable feature in modern western society with many different appliances. Everyone is familiar with its use in refrigerators and deep freezers. Air conditioning creates not only comfortable surroundings for men, but is also mandatory for the proper functioning of not-living things like mainframe computers.
The influence of low temperatures on varying body parts can be confusing; on the one hand an acute sports injury has to be treated with a cooling spray, preferably "on the spot", on the other hand a sore muscle caused by exposure to cold, has to be treated with the application of warmth.
Not only the danger of low temperatures like frostbite, but more its use for the treatment of various medical disorders have been known since the time of the earliest records. Its beneficial properties were entirely empirical based, like all ancient therapies. The use of low temperature, at first derived from snow and ice, was based on its anaesthetizing properties and slowing down biological processes.[1] Later, technical improvements made very low temperatures available which had potential killing and destroying abilities on living tissue. Since then, low-temperatures have found their use in virtual every specialty of medicine.

HISTORY OF MEDICAL USE OF LOW TEMPERATURES

For reasons of clarity and readability the following historical review is organized by chronicity with brief comments and references.

2500^{BC} The writing of the Edwin Smith Surgical Papyrus, later translated by *Breasted* mentioned the use of cold compresses to treat compound skull fractures and infected wounds.[2]
460^{BC} Hippocrates, the father of medicine, advocated the use of cold to control hemorrhage and to reduce swelling of painful joints.[3]
1050 An unknown Anglo Saxon monk employed cold as a local anesthetic.[4]
1570 Refrigeration anesthesia was known to Italian physicians.[5]
1661 *Thomas Bartholin* of Copenhagen described the use of cold as a therapeutic for all kinds of everyday illnesses.[6]
1665 *Robert Boyle* published a monograph on the influence of cold on living animals.[2]

Confronted with the above historical facts, *Bradley*[7] wondered: "and it is remarkable that the first physicians to investigate the use of cold within medicine are those from warmer climates. Presumably, the difficulties of producing low

temperatures in prerefrigeration times must have made these treatments as rare as modern-day techniques requiring esoteric and unproven drugs or medicines".
But the above mentioned properties of cold are still used in modern medicine; e.g. "coldpacks" for strained ankles and cooling spray as anesthetic to incise abscesses.

1714 *Fahrenheit* invented the mercury thermometer, later reinvented by *Réaumur (1739)* and *Celsius (1742)*.[8]

The invention of the thermometer is of considerable importance, because it was now possible to measure the actual "coldness" or temperature at which all the phenomena were happening. Furthermore the efforts to generate lower and lower temperatures could now begin. Scientists were now able to standardize their experiments and exchange results.

1787 *Spallanzani*: investigated the effects of temperatures of minus 24°C on insects, fish, amphibians, reptiles, birds and mammals. He also recognized the existence of water of subzero temperatures without the transformation into ice, a physical phase later called supercooling.[8]

1832 *Dominique J. Larrey*, a surgeon in the army of Napoleon, recorded during the retreat from Moskou that amputations could be done more or less painlessly providing the affected limb had been sufficiently cooled in the snow.[9] Local refrigeneration has been advocated as the anesthetic of choice for limb surgery as recent as 1991.[10-15]

1845 *James Arnott*, an English physician, published his first book on the therapeutic use of the local application of cold in a wide variety of conditions like headaches, neuralgia and more general diseases.[16] Arnott used salt solutions containing crushed ice in local applications at about -8 to -12°C to various body surfaces to freeze tissues.

1851 *James Arnott's* second book described the use of cold in the treatment of advanced cancers in accessible sites, such as the breast and uterine cervix. Treatment was done by irrigation with cold solutions, resulting in diminution of the size of the tumor, reduction in drainage and amelioration of pain.[17]

Thus Arnott is most probably the first who used cold for the treatment of malignancies.
Although he was not curing them, he considerably reduced the morbidity of cancer, especially pain, which sometimes is still a problem. The anaesthetizing characteristics of low temperatures were known, but its use to shrink, apparently destroying parts of the tumor was now recognized as a new effect of freezing.

1866 Local anaesthesia generated by a spray of ether was first described by *Richardson* and later replaced by ethyl chloride.[18]

This method became so popular that the term freezing is still synonymous in the English language with local anesthesia. This method of applying cold was a technical improvement and made experimental investigations possible. These soon followed.

1868 *Samuel* produced local freezing of the ear of a rabbit by means of an ether spray and described the subsequent clinical and microscopic changes.[19]

1883 *Openchowski* attempted to localize the physiological function of different areas within the cerebral cortex of dogs by local freezing. He obtained freezing temperatures using the evaporation of ether by a warm jet of air. Peripheral convulsions or paralyses produced by this method made functional mapping of the cortex possible.[20]

Until the beginning of the 20th century the "users" of devices producing cold were mostly also their "inventors". After the turn of the century these two professions became separated. To improve machinery, either for the development of cryosurgical instruments or the production of cryogenics a background with more engineering schooling was necessary.

1899 *Dr Campbell White*, an american surgeon stated: "Here and there during the past year or two liquid air has been used on several manifestations of disease, particularly carcinomata. The results has been glowing accounts of its power to abort and cure even malignant disease". He also noted that pure cultures of anthrax, diphtheria and typhoid bacilli survived immersion in liquid air for more than one hour.[21]

Furthermore Dr White considers "that we have reason to hope that we have in liquid air a therapeutic agent which will remove many otherwise obstinate superficial lesions of the body and cure some lesions which have hitherto resisted all treatment at our disposal, including the knife".[22]

White later reported again favorably on the possibility of cure of early epitheliomas and the palliative benefits in treatment of inoperable skin cancer.[23] He also quotes a colleague: "No treatment at our disposal could have destroyed an epithelioma of this character in so short time and with so slight a scar remaining as liquid air has done in this case".

Not all scientists were prepared to accept such confident statements.
The use of low temperatures was in this time in competition with more advanced techniques of surgery, especially since general anesthesia was now in widespread use. Opposition was often fierce as is shown in the July 1899 edition of *Scientific American*: "The suggested employment of liquid air as a caustic in surgical operations is a good example of the absurdities proposed by dishonesty or ignorance in order to impress the public".[24]
Nevertheless several physicians kept up the pace.

1907 *Whitehouse* used liquid air first as a spray. Later, because of the difficulties controlling the extent of the freeze lesion, he favored the use of cotton swab drained in liquid air, creating the first primitive form of a probe.[25]

1907 *Pusey* used solid carbonic (CO_2) snow and also liquid nitrogen for the treatment of benign tumors of the skin.[26]

1910 *Cold*, treating various skin diseases, favored the use of liquid air, but was forced to use carbonic snow because of technical difficulties in securing air in a liquid phase.[27]

1929 *Irvine* and *Turnacliff* gave a review of the literature on the use of cryogenic agents for skin disease up to that time. They emphasized that the use of a liquid oxygen spray made the need for applying pressure during freezing of skin lesions unnecessary, and thereby pain was reduced.[28]

These four physicians initiated a cryosurgical technique which is still in use. The simple treatment of warts by many general practitioners with cotton swabs dipped in liquid nitrogen is commonly practiced.
At this time liquid *oxygen*, which is capable of producing very low temperatures (-182,9°C) was used by several physicians. Unfortunately, safety considerations related to fire precluded more general use.

1930 In this year the first writing using the term "cryotherapy" to address the use of low temperature was published. *La Cryotherapy* by *Lortat-Jacobs* and *Solente* described several modalities in which cold or freezing temperatures were used in medicine, especially in dermatology and gynecology.[29]

The origin of the term cryotherapy, however, has been attributed to *Professor Bordos*, who used the term "cryocautery" in 1912 in association with his freezing apparatus and to *Giraudeau* who was supposed to have used the term "cryotherapy" in 1928.[30]
The use of low temperatures seems from the beginning of the twentieth century until the second world war an exclusive treatment for cutaneous diseases. Although there is one exception.

1938 *Dr Temple Fay*, frustrated by the problem of palliation in patients with inoperable cancer revived interest in the therapeutic effects of local cooling of tissues other than the skin. He treated a woman with intractable pain due to carcinoma of the cervix with massive pelvic extension. Refrigeration of the vaginal mass was achieved by inserting a hollow capsule connected with a continuous circulation of ice water. After 48 hours the patient was reported to be pain free and after 5 days devascularization and shrinkage of the mass was noted. The refrigeration was maintained for 5 weeks after which the patient's

condition had improved to such an extent that she insisted on leaving the hospital.[31]

1940 After *Fay's* initial promising experiences he employed cryotherapy on 124 selected patients with far advanced carcinoma; 19 patients died, 8 patients with metastases survived more than 5 years, but most important 95,7% were relieved of pain.[32]

The outbreak of World War II interrupted the development of cryotherapy. More significantly, after the war it became known that the technique of hypothermia was employed by German nazis on prisoners in concentration camps without anesthesia or preparatory treatment, thereby associating cryotherapy with other wartime atrocities. Local cooling was thus limited to external use and was principally employed in the treatment of skin diseases. Due to the limiting factor of instrumentation, cryotherapy of less accessible sites of the human body required further development.
A post world war II renaissance for a broader use of cryotherapy was initiated by a paper in the *New England Journal of Medicine*.

1963 *Cooper* described a newly developed cryosurgical apparatus using liquid nitrogen. "This machine now provides an ideal method of basal-ganglion surgery for Parkinson's disease.....and other disorders of involuntary movement has now been carried out....in a consecutive series of 800 cases". The article describes also the treatment of brain tumors and classifies the use of cryosurgery as "a new and significantly helpful approach to the problem of deep intracerebral gliomas and certain tumors at the base of the brain".
Furthermore: Inoperable cancer of the rectum was frozen with marked shrinkage of the tumor and immediate relief of local pain and obstruction.[33]

Most interesting are two editorials in the same journal commenting on "cold as a surgical instrument". The first gives a brief historical review of the use of cold suggesting that there is nothing "new". Although Cooper's new apparatus is acknowledged as "an important step in evolution" but one that "seems to warrant further trial and development in other fields of surgery".[34] Nevertheless, cryosurgery for the removal and destruction of brain, spinal and orbital tumors was successfully re-visited in 1992.[35]
Less friendly is the second editorial entitled *Current status of gastric freezing*. The author is not only discussing the new technique but also warns colleagues to employ the new technique without complete knowledge of risk, complications and ultimate value. Futhermore he states: "the temptation to use this new method for unwarranted financial gain cannot be ignored since there are alleged cases in which a fee equal to that for gastrectomy or a similar surgical procedure has been charged".[36]

The war had not only interrupted things, it also made new techniques available and soon science and medicine were booming. The application of low temperatures expanded to many scientific fields, each with its own developmental history:

Cryobiology: the study of the physical effects of low temperatures on living tissue.
Cryogenic Surgery, Cryosurgery: the destruction of tissue *in situ* through the local influence of low temperatures.
Cryotherapy: often used interchangeably with cryosurgery but has broader connotations covering all therapeutic uses of low temperatures. Cryosurgery is a form of cryotherapy, as is the use of cold packs to prevent tissue swelling. It seems further appropriate to use the term cryo*therapy* when the application of low temperature is the only performed treatment, for example: the freezing of skin lesion. The term cryo*surgery* should be reserved for the use of low temperatures as it is part of a surgical procedure.
Cryopreservation: The permanent cooling of living tissue to preserve its use at a later time. This science made, for instance the extended storage of blood, blood derivatives and semen possible. As important as this development was for modern medicine it will not further be discussed, because it is beyond the scope of this thesis.
Hypothermia: The lowering of the *body* temperature of the normal homeoterm man below 35°C. Lowering the bodies core temperature modifies the internal metabolic environment. In combination with anaesthesia it reduces metabolism and oxygen needs to such an extent that it permits the interruption of circulation safely for longer periods of time. It facilitated cardiac surgery, making direct repair of certain lesions possible.[37]
Cryogenics: The science which is engaged in the development of freezing temperatures within a biological system.

THE HISTORY AND DEVELOPMENT OF CRYOGENICS AND CRYOSURGICAL INSTRUMENTS

Progress in the attainment of low and very low temperatures is a reflection of the technical inventions and advancements throughout history. In looking back the apparatuses used in the early days of cryotherapy seem somewhat contrived. On the other hand modern cryotherapy instruments, which are perfectly equipped for successful treatment today, will probably be deemed inadequate tomorrow. In this cryotherapy is comparable to every other advancement in medicine. Therefore continuing research to improve current techniques is necessary, in particular to answer demands for safety and expanded indications.
Acquiring low temperatures for therapeutic applications in medicine has not been difficult for medical specialists. Most of the technology was adapted from other industrial developments and breakthroughs.

1851 *Arnott* was the first to use some kind of instrument for applying cold. The technique was based on cold coming from a freezing mixture of ice and salt kept in a metal container. From this a rubber tube was connected through which the solution was transported to specially designed rubber cushions. These cold cushions were held against the body parts to be treated. Temperatures as low as -24°C were achieved.[17]

1868 A more practical form of applying low temperatures was the use of ether and later ethyl ether as a spray, however these are potentially explosive materials.[18]

The real breakthrough in achieving very low temperatures was the ability to liquify and store various gases.

1877 *Gailletet*, a french engineer, liquefied small quantities of oxygen and carbon monoxide by expansion of the gases under high pressure.[38]

1883 *Wroblewski* and *Olszewski* converted oxygen and nitrogen into a liquid state.[39]

1895 *Von Linde* applied the Joule-Thompson principle to liquify larger quantities of air and extract of liquid nitrogen from it.

Von Linde's liquefaction process begins with compressing water cooled air. This cool compressed air is than further cooled countercurrent to outgoing cold products, which are normally the waste products of the separation process. The cool compressed air is than throttled through an expansion valve. It is here that the Joule-Thompson principle becomes effective: the expansion of a gas or vapor through a restricted orifice will lower its temperature. At this lower temperature, some of the air will liquefy, and can be collected in a container. The liquid air can be run through a fractioning column and separated into its various components by utilizing their unique boiling points.

1898 The storage of liquid gases extracted from air in a special container was made possible by its inventor's name: *Dewar*.

The Dewar storage container and principle are still in use. The liquid gas is held in a container with maximum isolation from its surroundings by virtue of a vacuum double wall. In this fashion warmth is withheld from the liquid gas preventing evaporation. Storage is possible under normal atmospheric pressures. The container is closed by a foam plug. Under these conditions liquid gas will only evaporate in small percentages; 1-8% per day, depending on the gas, and the size and quality of the container. By replacing the foam plug with an adjustable valve, to which a pressure relief and a liquid withdrawal device are added, the liquid can be kept under a predetermined pressure, thereby permitting convenient withdrawal of liquid from the container. If large amounts of liquid need to be extracted in a short time, the pressure can be raised by a heating

device built into the container. As various liquid gases became available at the beginning of the twentieth century, the development of instruments and accessories to apply them clinically began.

1907 The earliest instrument was designed by *Whitehouse*.[25] The principles he devised are still used in modern hand held liquid nitrogen spray units (Figure 1.1).

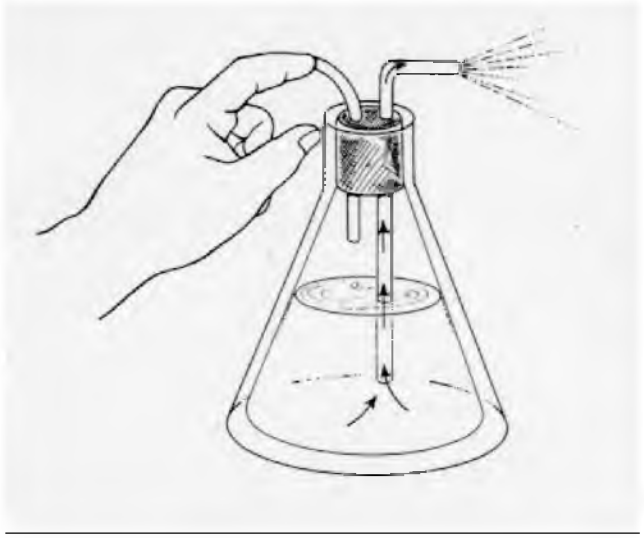


Figure 1.1: By blocking the short outlet, pressure in the bottle is allowed to build because o f vaporization of the liquid, which will force liquid trough the long tube as a spray.

Although the liquefying of different gases was technically possible, it was not generally available. Until the second World War other means were employed.2

1907 Because *Pusey* had difficulty in obtaining liquid air he was forced to use carbon dioxide snow (-78°C). Carbon dioxide was held in the liquefied state by the use of high pressure. When the liquid carbon dioxide was released into the air, the decrease in pressure caused freezing and the formation of a white snow, which was collected in a leather bag. The snow was then compressed into appropriate shapes (sticks) for application to the skin.[26]

1930 *Lortat-Jacops* and *Solente* used copper tips of various sizes connected to a CO_2 source.[29]

1942 *Poppe* used frigid air forced under pressure through a copper tube packed with CO_2.[40]

1943 *Carpenter* devised copper probes cooled by solid CO_2 pencils.[41]

1950 *Allington* introduced the use of liquid nitrogen into medical practice. He used cotton swabs dipped in liquid nitrogen.[42,43]

The limitations of the liquid nitrogen-soaked cotton applicator and solid CO_2 were defined by *Grimmett* who studied frozen tissues microscopically. Liquid nitrogen applied in this fashion induced cell death at a maximum depth of 2 mm and CO_2 even less.[44]

1961 *Cooper* introduced an automatic cryosurgical apparatus, which used liquid nitrogen in a closed system, and which permitted continuous and rapid freezing of tissue. Furthermore it featured controls for regulating temperature at the tip of the probe.[45,46]

1966 *Zacarian* used solid copper cylinder discs, cooled by immersion in liquid nitrogen. Their thermal capacity was much better than cotton swabs dipped in liquid nitrogen and cell death up to 7 mm from the disc was possible.[47,48] This was an improvement, but the freezing of large quantities of tissues was not possible.

After 1960 a variety of cryosurgical instruments were designed and employed a range of cryogens. All designs have special adaptations and auxiliary equipment for the specific clinical application. For instance, the probe to perform an intracapsular cryoextraction of a lens of the eye is completely different compared to the probe used for the treatment of bone tumors.

The increase of general interest in the use of cold temperatures has led to the foundation of several organizations.[49,50] The most widely known and their activities are listed below:

1964 The Society for Cryobiology, publisher of the journal *Cryobiology*.
1968 The Society of Cryosurgery, publisher of the *Journal of Cryosurgery* from 1968 until 1969.
1974 The Japan Society of Low Temperature starts publishing the journal *Low Temperature Medicine.*
1974 The International Society of Cryosurgery organizes meetings with a 3 year interval.
1977 The American College of Cryosurgery. It has held meetings almost annually.

Today about 100 articles concerning the use of low temperatures in experimental work or clinical applications in different specialties are published in the English literature every year. In the non-english literature, especially Russian, many papers are available as abstracts on MEDLINE EXPRESS. This demonstrates that interest in every aspect of the use of low temperatures is widespread.

CHAPTER 3

CRYOPROBE DESIGN, COOLING POWER, BASIC TECHNIQUE AND MONITORING

CRYOPROBE DESIGN

The basic design of cryoprobes can be divided into open and closed systems. In general, closed systems employ two different principles for creating low temperatures at the end of a probe. Since today liquid nitrogen is most commonly used, this section will deal specifically with this particular cryogen.

CLOSED SYSTEMS:

A. Boiling at the end of a probe:
   The first principle to cool a cryoprobe is allowing liquid nitrogen to boil at the end of the tip of the probe; for boiling it extracts latent heat from its surroundings, cooling it at the same time. As long as liquid nitrogen is passed through the tip fast enough to maintain boiling, the temperature of the tip of the probe will remain at the boiling point of liquid nitrogen: -195,8°C (Figure 3.1). The liquid nitrogen has to be stored in a Dewar container. As the very cold liquid nitrogen is transported to the probe, a substantial part of it will boil due to all the warm hoses and pipes it passes. Initial performance will therefore be compromised and improves only after the entire transport system is precooled, which takes some time. The cool exhaust is therefore rerouted through the probe. To make sure that only the tip of the probe is freezing, extensive isolation of the remaining probe and hose is necessary with in addition to the Dewar container makes the system expensive.

B. High Pressure Probes:
   The other principle to cool the end of a cryoprobe in closed systems utilizes the Joule-Thomson effect. If a pressurized gas is allowed to expand to a much lower pressure, its temperature will drop (Figure 3.2). The magnitude of change in temperature depends on the change in pressure and the physical characteristics of the substance used. The most commonly used gas in this kind of probe is nitrous oxide.
   The size of the orifice, which facilitates the pressure drop, is crucial for a proper operation and performance of the instrument. After expansion the now cold gas is transported back along the hose and can cause freezing of the probe. To avoid this isolation of the probe is necessary. A further problem is that as long the probe is used the pressure in the storage cylinder drops. To regain pressure some of the liquid nitrogen has to boil, extracting latent heat from the liquid nitrogen left in the storage cylinder, which in its turn cools down causing a decrease of pressure.

High pressure probes are less powerful in cooling, but much less expensive compared to liquid nitrogen probes.

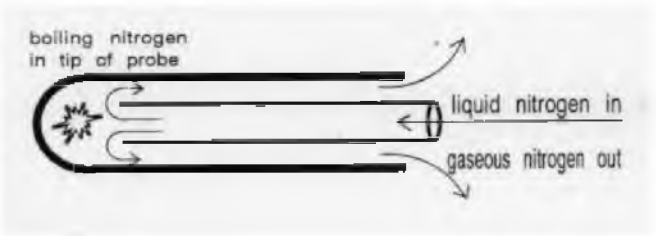


Figure 3.1: Closed cryoprobe system, cooling of the tip is achieved by boiling liquid nitrogen in the tip of the probe. [51]

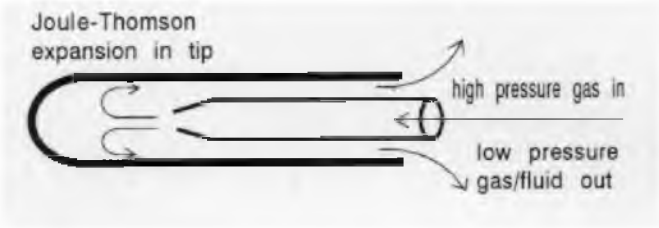


Figure 3.2: Closed cryoprobe system, cooling of the tip is achieved utilizing the Joule-Thomso n principle, [51] see text.

OPEN SYSTEM:

A. Liquid Nitrogen Sprays:

Spraying liquid nitrogen directly on tissue is an effective, if not the most effective way of cooling. The liquid nitrogen cools the tissue by boiling, which occurs as heat is extracted from the tissue surface. In this system liquid nitrogen has to be transported to the nozzle, therefore this device needs the same precooling and thermal isolation as closed liquid nitrogen cryoprobes. When the liquid is forced out of the nozzle, the sudden drop of pressure causes partial vaporization, a phenomenon called "flashing". Higher original driving pressure induces more vaporization, impairing the cooling potency of the spray. On the other hand pressures too low will transport only limited amounts of liquid nitrogen to the spray nozzle.

Liquid nitrogen drops in the spray will start boiling immediately when coming into contact with a higher surface temperature. The initial vaporized gas can form a vapor layer between the liquid nitrogen and the target tissue. This vapor layer or "film" behaves as an insulator and prevents further cooling of the surface. This form of boiling, called filmboiling, can also occur in the precooling phase, because the inner surfaces of the hose and probe are still relatively warm. Filmboiling causes a pulsatile appearance of the spray. Filmboiling will stop only when the complete system is precooled to -175°C.

Most systems are equipped with a small electrical heater in the tip of the probe making defrosting possible facilitating its easy release from the frozen tissue. The operational control of cryoprobes in general is carried out by simply stopping the flow of cryogen. Stopping the cryosurgery is a decision made by the physician. The decision is mainly based on experience. In addition, monitoring devices are available, which will be described below.

COOLING POWER

Cooling power of a cryoprobe is defined as the generating of the lowest temperature and the time to maintain this temperature.
There are several extrinsic and intrinsic factors which influence the performance of a cryoprobe. The intrinsic factors are to a certain extent under the control of the physician. The extrinsic factors are related to the tissue being treated.

INTRINSIC FACTORS:

A. Temperature of the tip of the cryoprobe:
   As stated above liquid nitrogen probes can produce temperatures as low as -196°C and high pressure probes -80°C. Figure 3.3 shows the size of an ice ball generated by different tip temperatures after a freeze time of 3 minutes. Low tip temperatures also induce a steeper temperature gradient, which is more destructive to tissue than a slow freeze to the same temperature. This phenomenon will be discussed in detail in chapter 4. Liquid nitrogen sprayers produce tissue surface temperatures below -175°C.

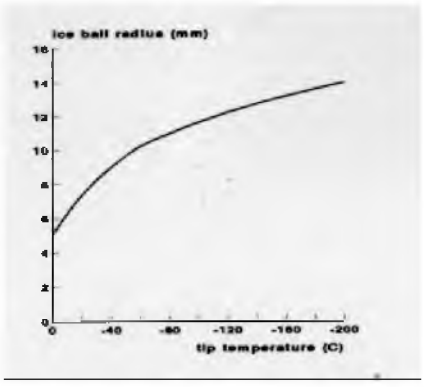


Figure 3.3: The effect of tip temperature o n the ice ball size achieved by a 5 millimete r radius probe in 3 minutes. [51]

B. Duration of freeze:
   This is the intrinsic factor which is most easily controlled by the physician. As long as the cryoprobe is able to maintain a low temperature, the size of the cryogenic lesion will grow, although there is a certain maximum. Figure 3.4 shows the size of an ice ball plotted in time around a 5 millimeter radius probe at a temperature of -150°C. After an initial rapid expansion, there is a more gradual increase in iceball size, until a steady state is achieved. At steady state the amount of heat being extracted by the probe is balanced by the heat supplied by the surrounding tissue.

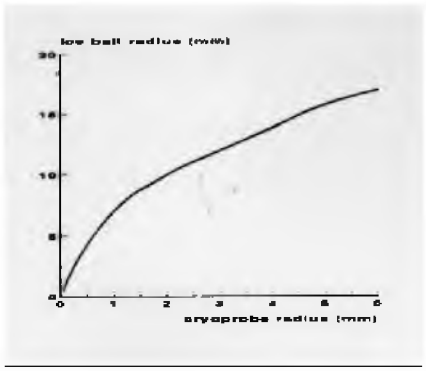


Figure 3.4 (left): The effect of cryoprobe radius on the size of ice ball achieved in 5 minutes for a tip at -196°C.[51] Figure 3.5 (right): The growth of an ice ball around a 5 millimeter radius probe at -150°C.[51]

C. Contact area between probe and tissue:
Increasing the contact area between probe and tissue enlarges the size of the iceball formed around the probe (Figure 3.5).

The *effective* area of contact of a liquid nitrogen sprayer is as large as the wetting area of the sprayer showing obvious freezing. Filmboiling, as explained above, will also occur when liquid nitrogen is sprayed on warm tissue. Liquid nitrogen droplets, supported by the vapor layer will than tend to flow across the surface and may extend to tissue out of the target area, causing unwanted freeze lesions. As soon as tissue temperature drops below -175°C, filmboiling will stop.

EXTRINSIC VARIABLES:

A. Tissue thermal conductivity: All biologic tissues have unique thermal conductivity properties. The thermal conductivity of any tissue is defined as the Joules of energy needed to induce a temperature difference of one degree Celsius over a distance of one centimeter in one second.

B. Tissue density: Tissue density, which is the amount of tissue (grams) per volume (cubic millimeter). It has a direct influence on thermal conductivity.

C. Tissue specific heat capacity: This capacity of tissue is defined as the amount of energy (Joules) obtainable from one gram of tissue per degree (Celsius).

D. Tissue metabolic heat: This is defined as the energy which one cubic millimeter of tissue is able to produce in one second by elevating its metabolic rate. Elevation of metabolic activity as reaction to cooling is a normal cellular "first aid" response.

E. Blood perfusion: The perfusion of blood is regulated by the organism involved. When bloodflow to the area frozen is high the effect can be considerable, because of the extra heat source it provides. In some practical situations, when a lesion is located on an extremity the physician can block this extra heat source by applying a tourniquet to the extremity, thereby inducing local circulatory arrest.

BASIC TECHNIQUE

The basic medical principle that any therapy should be maximally effective with a minimum of morbidity also applies to cryosurgery. An optimally performed cryosurgical treatment should only produce a predictable and predetermined area of tissue necrosis. Because the development of cryosurgical instruments has been guided by this principle, today a suitable instrument is available for almost every cryotherapeutic application. Current emphasis is thus directed to maximizing effectiveness with monitoring and avoiding local and/or general morbidity.
The basic technique of cryosurgery concerns two different issues:

A. An effective use or exploitation of biological mechanisms leading to cell death under the influence of low temperature. It has been shown that the most effective way to achieve this is rapid freezing and slow thawing, done in repetitive cycles.

B. To establish the suitable cryobiological circumstances mentioned under A, the freezing of tissue requires an efficient technique *in situ* to extract heat from the tissue.

The requirements for *rapid freezing* are:

A. A cryogen suitable for the lesion, not only providing potential cooling power but also in sufficient quantities. Furthermore it must be safe (nontoxic and nonflammable), easy to store and transportable, and preferably inexpensive. For orthopedic purposes only liquid nitrogen meets all these criteria, either used in closed probe systems or as a spray.

B. The contact area between the lesion and the cryogenic device should be as large as possible facilitating rapid transport of heat. The surface of a lesion in orthopedic oncology is always irregular and frequently large. These surface properties nearly always necessitate the use of a liquid nitrogen spray instead of a probe (Figure 3.6).

The most lethal factor for cells is the maximum reached subzero temperature. The basic question to hold the tissue for a certain period in the frozen state at a lethal temperature before thawing is not yet answered. Commonly prompt thawing is allowed when a preselected temperature has been reached.

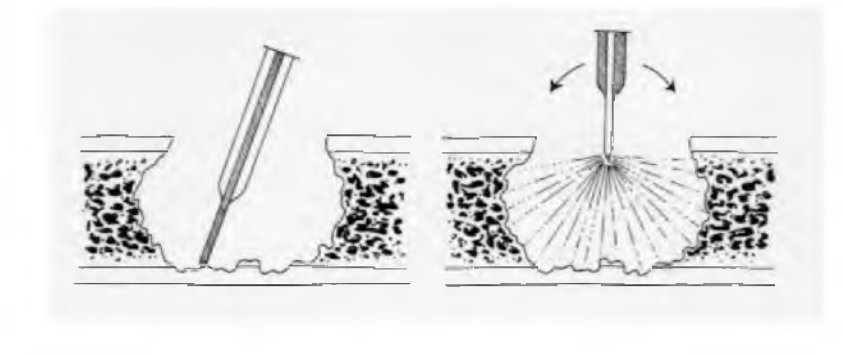


Figure 3.6: A cryoprobe (left) is not able to freeze an irregular surface like spongiosa, a spray will wet the complete lesion (right).

The principle for *slow thawing* requires only patience on behalf of the surgeon. Ideally frozen tissue should be allowed to completely thaw without assistance. While rapid freezing can be achieved in less than 30 seconds, spontaneous thawing in the orthopedic setting can take up to ten minutes or more. The thawing rate is most influenced by nearby heat sources such as blood vessels. In order to achieve a slow thaw rate, the use of a tourniquet to induce circulatory arrest, when possible, is appropriate.

The necessity for *repetitive freeze and thaw cycles* is explained in chapter 4. Performing them is a technical matter affected principally by the capacity of the chosen equipment. The optimal interval between cycles has received little attention in the literature. In general additional cycles are begun after the frozen target tissue has warmed to above 10°C.

When a lesion is selected for cryosurgical treatment care should be taken to ensure that an adequate margin of normal tissue is included in the freeze injury. When a lesion is too large for a single freeze, it may be frozen in sections, with each section overlapping the other.

The operative technique of cryosurgery in orthopedics is described in methods and patients, chapter 10, page 87.

MONITORING

A cryosurgical procedure with a satisfactory result can be achieved by using only the physician's clinical judgement and experience. Typically in freezing soft tissue lesions, the progress of the treatment can be followed by observation and palpation. The depth of freezing is most difficult to access clinically and can be estimated by observing the lateral spread of freezing in the target tissue.[52] Although clinical judgement of freezing extent is reasonably accurate, it is probably not enough to perform "state of the art" cryosurgical procedures. There are several reasons to use more precise monitoring devices:

A. To ensure that lethal temperatures are reached. The temperature of frozen tissue cannot be determined by its appearance as frosted tissue looks the same at any freezing temperature.

B. An accurate measurement of the depth of the freezing is important not only for obtaining adequate margins, especially if the lesion has a malignant nature, but also to avoid an unwarranted extension of the freezing and potential morbidity.

C. Local temperature measurement enables a more precise determination of the ending of the thawing phase.

D. Not only is local monitoring important, but systemic monitoring is also recommended, since cryosurgery has been associated with potentially lethal circulatory and pulmonary complications.

E. Monitoring and preferably recording of the cryosurgical procedure enables the physician to evaluate the procedure itself, for instance the freezing rate and better interpret follow-up results with respect to the procedure. Adjustments in technique can be developed and introduced. Scientific research on data will ultimately improve the quality of cryosurgery.

F. When the whole freezing procedure is recorded it provides written evidence which can be of medicolegal importance.

MONITORING DEVICES:

To supplement clinical judgment during cryosurgery a range of monitoring devises and techniques has been developed. Many of these have been developed to address monitoring needs specific to individual applications of cryosurgery.

A. Thermocouples:

Thermocouples are formed by a series of two dissimilar conductors, for instance iron and constantan, in a closed circuit. When the junction of the two metals is subjected to a different temperature from the rest of the circuit, an

electromotive force proportional to the difference in temperature is generated. This voltage can be measured. The thermocouple is commonly mounted in the tip of a hollow needle to facilitate its use. Thermocouples were first used to monitor cryosurgery of skin lesions. Their importance was recognized early in cryosurgical practice, particularly in establishing lethal temperatures.[53] The accuracy of the thermocouple readings is important as the effectiveness of treatment partially depends on it. Proper calibration and reliable hardware (good quality of thermocouple, wiring, electrical connections and display devices) are imperative. Even more critical is the correct placement of the thermocouple itself: a one millimeter variation in the thermocouple positioning can represent a 10-15°C temperature difference,[54] and checking their position with radiographs is sometimes necessary (see chapter 11). Also if the needle shaft passes through a frozen area, conductance of heat may result in falsely low readings.
Extraneous heat sources in contact with any part between the tip of the

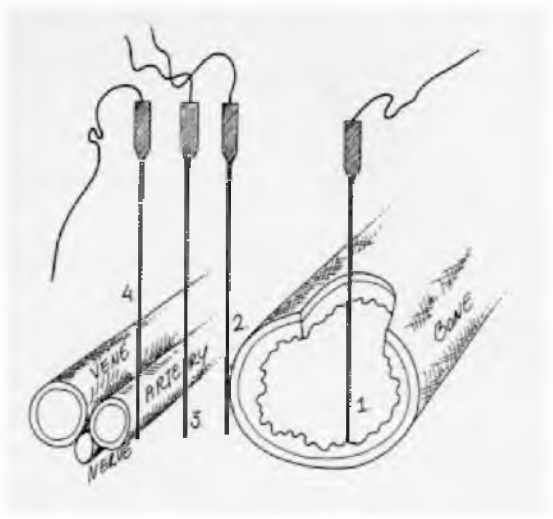


Figure 3.7: Thermocouple 1 is situated intralesional; 2 extracortical, adjacent to the lesion; 3 between the lesion and the vascular bundle and 4 close to the vascular bundle.

thermocouple and the recorder can also alter the reading.[55,56] Preferably several thermocouples are in situ at different locations.
Measuring temperature with thermocouples is helpful in performing the following important functions (Figure 3.7):
* to establish lethal temperatures in the frozen lesion itself.
* to achieve sufficient margins at the edge of the lesion.
* to avoid freeze injury of structures nearby (neuro-vascular bundle).
* it gives information about freeze and thawing rates.

B. Tissue impedance and resistance measurements:
Normally unfrozen tissue is a conductor of electricity. During freezing electrical conductivity decreases due to the removal of water as a result of the formation of ice. When all extracellular water is frozen, electrical resistance rises rather abruptly to high levels. This change is known as "eutectic freezing" and is interpreted as being indicative of freezing sufficient to induce cell death. This technique of monitoring can only be used in soft tissues. In the past a wide range of tissue temperature values have been observed in relation to electrical impedance changes causing concern about the reliability of this monitoring technique.[57-60]

C. Thermography:
Special cameras capable of measuring infrared radiation from the body surface can be used to define isotherms down to -100°C, visualized in a thermogram. During freezing thermography can ensure that the whole lesion is within the appropriate lethal isotherm.[61,62]

D. Ultrasound:
When water is frozen its density decreases about 10%. This increases the transmission of sounds and distinguishing it from unfrozen areas is possible. The technique is only employable on surfaces where direct contact between the ultrasound probe and tissue is possible such as the skin and liver.[63,64] That stipulation prevents its use in orthopedic oncology.

E. Computerized Tomography:
The principle of this monitoring technique is based on the phase change of water during freezing and the resulting alteration in its density. It currently is used in cryosurgery of the brain.[65] The logistics and cost of intraoperative CT monitoring sharply limits its use in orthopaedic oncology.

F. Magnetic Resonance Imaging:
After the development of MRI compatible cryosurgical instruments,[66] data were published describing the use of MR as monitoring device during cryosurgery in order to visualize the extent of the freeze not only in relation to the temperature achieved,[67] but also to the histological outcome.[68] Specific post-cryosurgical MR appearances of bone tumors were described.[69]

CHAPTER 4

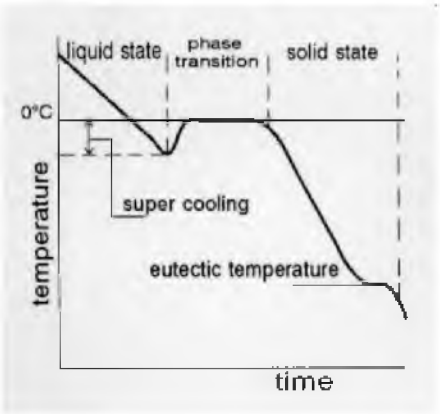
CRYOBIOLOGY AND IT'S EXPLOITATION TO INDUCE CELL DEATH

To understand the effects of cooling, freezing and thawing on the biology of living cells, it is mandatory to review the physical changes occurring during freezing to the main component of tissue; *water*.

The state or phase (vapor, liquid or solid) of water depends on temperature, pressure and volume. The liquid and solid phase of pure water are in equilibrium at atmospheric pressure and 0°C. By increasing pressure this temperature (0°C) or freezing point can be lowered. This phenomenon of pure water with a subzero temperature is known as supercooling.

When its temperature is lowered, pure water will shift to a solid state by either vitrification or crystallization. Very rapid cooling of pure water will induce vitrification which entails the formation of amorphous, transparent, glasslike structures rather than crystals.[70] Crystallization requires initiating nuclei, for instance an insoluble crystalline impurity.[71] Slow cooling rates of water (< 1°C/min) will induce large crystals around a few nuclei. During fast cooling rates many small crystals are formed which are thermodynamically unstable and tend to join each other by recrystallization to minimize their surface energies.[72]

During freezing of *solutions*, ice crystals remove more and more pure water from the solution, elevating the dissolved solute concentration and lowering the vapor pressure of water to that of ice at the same temperature. In this situation solid and liquid phase coexist and is, as mentioned earlier called supercooling. The supercooled phase ends with a sudden rise of the temperature due to dissipation of latent heat generated by the recrystallization of the thermodynamically unstable small crystals. The temperature at which both solute and solvent will become solidified is called the eutectic temperature (Figure 4.1).



changes in a system which is continously further cooled in time; see text for explanation.

FREEZING OF TISSUE

The freezing of tissue is more complicated since its solvent (water) is divided by cell membranes into extracellular and intracellular compartments. Cell membranes in general easily allow the passage of water, but far less readily allow passage of other solutes.
When tissue is subjected to a constant *slow* lowering of temperature it first enters a supercooled phase without ice formation. Temperatures of 10-15°C below zero will initiate ice formation in the extracellular compartment. The intracellular compartment remains unfrozen because it's milieu contains substances with high and low molecular weight, which lower freezing temperatures. Due to the freezing of water in the extracellular compartment concentration of solutes will rise, creating an osmotic pressure induced transport of water from the intra- to the extracellular compartment. This loss of water will lead to shrinkage of the cell, accompanied by higher concentrations of the solutes, which further prevent the formation of ice in the intracellular compartment.[73] This shrinkage and high concentration of solutes, especially of salts, may be responsible for cell injury during slow cooling.[74]
Very *rapid* cooling induces intracellular ice formation,[75] because there is insufficient time for water leaving the cell to maintain osmotic equilibrium across the cell membrane. Intracellular ice formation is believed to be lethal to the cell. Based on histological investigations it has been shown that intracellular ice causes mechanical damage to the membrane,[76] and disturbs the function of mitochondria[77] and other cell organelles and membranes.[78-81]
The injury to cells occurring during rapid cooling is called thermal shock.

THAWING OF TISSUE

During thawing the "behaviour" of the ice crystals is dependent on the rate of thawing. In contrast to rapid thawing, slow thawing is accompanied by recrystallization and the crystals can grow to damaging sizes.[82] The damaging effect of intracellular ice crystals, only formed during rapid freezing can therefore be exploited a second time, if slow thawing is allowed, thereby enhancing recrystallization. On the other hand, if tissues have been cooled slowly, causing shrinkage and intracellular dehydration, rapid thawing may be damaging because the cells are exposed to high electrolyte concentrations.[83]

MICROCIRCULATORY FAILURE IN FROZEN AND THAWED TISSUE

After thawing there is typically a brief period of vasodilation. Additionally the endothelium of blood vessels is particularly sensitive to freeze-thawing, leading to increased permeability of vascular walls, interstitial edema, slowing of

circulation and platelet aggregation. Capillary obstruction and vascular stasis ensues resulting in tissue ischemia and cell death.[84,85] The importance of postthaw ischemia was demonstrated in an experiment in which carcinoma cells transplanted directly after being subjected to cryosurgery would grow in the host, but did not survive if transferred 48 hours after the cryosurgery. Histological examination of these tumors revealed widespread vascular thrombosis.[86] In bone, microangiography has demonstrated a total avascularity of the cortex to cryosurgery.[87]

The loss of blood supply in cryosurgically treated tissues deprives all cells of any possibility of survival. Ischemia results in uniform necrosis of tissue, except at the periphery of the lesion.

THE VALUE OF REPETITIVE FREEZE THAW CYCLES

It is necessary to repeat the freeze and thaw cycles several times because living tissue is capable of resisting thermal injury and it is technically difficult to achieve optimal conditions for cell death in all areas of many lesions. To compensate, repetition of freeze thaw cycles is a practical solution and creates safety especially at the periphery of the lesion. After the first cycle, thermal conductivity in the tissue is increased, and the specific heat capacity and vascularity are decreased. This pre-conditions the tissue, making the next cycles more effective by virtue of faster cooling and slower thawing rates. The benefit of repeat cycles is well established in the literature.[88-91]

HOW LOW IS THE LETHAL TEMPERATURE?

The answer to this question depends upon where the temperature is measured: close to center of the lesion and the cooling source, or at the periphery where temperatures may be higher. With this thought in mind the exact temperature which is supposed to be lethal for cells has been lowered during the last 50 years. Whereas a temperature between -10 to -20°C was thought to be sufficient in 1949,[92] it was soon turned into less than -20°C.[53,93] Authors of later experiments on animals advocated temperatures between -20 to -30°C.[94] In some experiments in vitro total cell death was achieved only with temperatures of -40 to -50°C.[85] In treating cancer cells the minimum in vivo temperature advised is -50°C.[90,96-98] In 1979 -30°C was thought to produce a marginally lethal injury. Therefore a safer technique was proposed especially for neoplastic tissue. It required -40°C in *normal* tissue surrounding the lesion.[99] More recent the -60°C isotherm beyond the periphery of the lesion is accepted as adequate treatment.[100]

In summary, cryosurgery is most effective in inducing tissue necrosis when the following features are employed:

- rapid cooling to induce intracellular ice formation
- temperatures as low as -50°C
- slow spontaneous thawing creating intracellular recrystallization
- repetitive freeze thaw cycles using the "conditioned" tissue properties of previous cycles.

There is also some evidence[101] that this program should be further modified by maintaining the tissue in the frozen state for several minutes as is shown in Table 4.1

PROGRAM		TEMPERATURE		
		-15 to -24°C	-25 to -35°C	-36 to -50°C
I	fast/fast	23.5	21.7	66.7
II	fast/slow	55.5	62.5	87.5
III	fast/hold/fast	50.0	65.3	100.0
IV	fast/hold/slow	72.7	93.1	100.0
V	slow/fast	0	31.5	50.0
VI	slow/slow	28.6	64.7	100.0

Table 4.1: The tissue kill rate (%) in several programs of freezing and thawing with or without holding.

CHAPTER 5

A LITERATURE REVIEW OF CRYOSURGERY WITH SPECIFIC REFERENCE TO THE SKELETAL SYSTEM

A careful review of the literature reveals that cryosurgery is not as generally accepted in the treatment of diseases of the musculoskeletal system as it is in other categories of disease such as dermatologic disorders.[43] It has been adopted only by a handful orthopedic surgeons. However, its use for bony pathology of the maxilla, mandible and facial bones is more commonly accepted and has resulted in a substantial body of basic research.
It seems that cryosurgery for orthopedic pathology is more generally practiced in Russia, considering the many (very) brief English abstracts appearing in Medline Express. Unfortunately the original articles are published in Russian Journals, and are not easy available.

EXPERIMENTAL DATA ON CRYOSURGERY OF BONE

Extensive research has been done to establish the histological changes of bone after it has been subjected to low temperatures.
Gage and Emmings (1967) produced freezing injuries in canine femurs and mandibles in situ by coiling a latex rubber tubing around the bone through which liquid nitrogen was allowed to flow at a high rate. The animals were subsequently sacrificed at various intervals and the bones removed. Histological examination demonstrated that the full extent of the freezing injury was only evident after several days. Osteocytes were slow to disappear, but within seven days the frozen bone contained no living cells. However, after a few days, repair was seen in the form of osteogenesis initiated by vital bone and periosteum at the border of the devitalized segment. Dead bone was slowly replaced by vital bone and after one month a thin layer of trabecular subperiosteal new bone covered the nonvital shaft. In time this layer thickened and at approximately four months a strong sleeve of compact bone enclosed the devitalized segment. The reparative changes of the medullary cavity began earlier, but ended later when compared to the subperiosteal repair. Between one and two months revascularization was apparent and the bone was weakened by resorption. Fractures of the femurs were common during this time. Long term observation indicated that the whole process of resorption and revitalization ending in complete repair took about one year.[102]
These histological sequences were acknowledged by *Hausamen (1973)* who froze the mandibles of rabbits and by *Schargus et al (1975)* who froze rabbit tibias.[103,104] The sequence of radiographic features observed during these experiments began within two weeks. Initially repair was seen as periosteal

thickening at the border of the frozen segment, which grew larger and finally covered the whole lesion. The radiologic structure of the frozen bone did not change during the first four weeks. Afterwards slow resorption of the dead bone was seen as delicate subperiosteal translucent areas appearing in the frozen segment, until the whole frozen segment was replaced by new bone. This process of radiographic remodelling in rabbits took about 12 weeks. It has been shown equal in dogs, but in this species it took more time, up to 6 months.[105]

Marcove (1971) suggested that bone responds to freezing in a special manner whereby the cellular elements are destroyed but not the calcified matrix so that, unlike soft tissue, the structural integrity of bone is maintained.[106]

Kuylenstierna et al (1980) investigated the early vascular changes after cryosurgery in the rabbit mandible with microangiography. After 30 minutes a total avascularity of the cortical bone corresponding with the cryosurgically exposed area was seen. After 48 hours, however, the avascular area far exceeded the cryosurgically exposed area and extended into the soft tissue surrounding the bone.[107] These results further supported the hypothesis that postcryosurgical ischemia is a major cause of cell death. Two weeks after cryosurgery the marrow cavity became filled with dilated and tortuous vessels, which initiated a recanalization of the old haversian canals and retained their normal size and number after 12 weeks. Cortical vascularity returned to normal after 24 weeks.[87]

Kuylenstierna et al (1981) proved in further experiments using fluorochrome labeling that early (four weeks) revitalization of the medullary cavity occurred in concurrence with his angiographic results, thus demonstrating the importance of intramedullary (endosteal) osteogenesis.[108]

Bradley et al (1975) defined three post-cryosurgical phases: necrotic, osteogenic and remodelling. Furthermore, he suggested that cryosurgery of some neoplasms could obviate radical resection of bone and the need for reconstruction. To test the efficiency of cryosurgical treatment he compared several different cryosurgical techniques and monitored the results with thermography. He concluded that the use of a liquid nitrogen spray was most effective, allowing rapid freezing of large volumes of bone despite irregular surfaces.[62] In this respect he also demonstrated the shortcoming of a cryoprobe.

Kerschbaumer et al (1980 and 1984) advocated a cryosurgical technique for bone in which an intramedullary cryoprobe was introduced adjacent to the lesion through a cortical window. This method has some disadvantages. First, direct visualization of the lesion is not possible. Also, a cortical window placed next to the lesion treated with cryosurgery further weakens the bone and frequently makes osteosyntheses necessary.[109,110]

In an effort to find an alternative for high condylectomy in the management of painful degenerative arthritis of the temporomandibular joint, *Marciani et al (1986)* performed a cryosurgical lesion of the mandibular condyle in monkeys. The structure of bone remained intact and revitalized over time but the articular cartilage was irreversibly damaged.[111]

Lenz and Preussler (1975) and *Schneider (1981)* proved respectively in immature rabbits and dogs that the epiphysis of long bones subjected to cryosurgery will result in its arrest and or growth disturbances causing severe deformity of the limb.[112,113]

One of the most interesting experiments involving the therapeutic effect of cryosurgery on murine osteosarcoma was conducted by *Müller et al (1985).* Artificially induced osteogenic sarcomas in the hindleg of mice were treated with either cryosurgery, local resection or amputation. Cryosurgically treated mice had significantly fewer metastases compared to amputation, which was felt to be related to a cryosurgically induced immunological protection, although measurement of immune parameters could not sustain this claim. Local resection yielded the poorest results with 100% local recurrence and the greatest number of metastases. Transplanted tumor material treated with one cycle of cryosurgery produced new tumors in 80% of the hosts, while tumor material treated with two cycles of cryosurgery could not produce any tumors after transplantation.[114]

The effect of cryosurgery on the strength of bone was tested by *Fisher et al (1978)*. The mandibles of rats had a reduction in strength of approximately 30% eight weeks after cryosurgery. The gradual loss of strength in these bones paralleled observed radiographic osteolysis. At four months the mandibles had regained strength accompanied by clear radiographic evidence of sclerosis.[115] Although not investigated in this experiment, the gradual loss and return of strength in cryosurgically treated bone also parallels histologic evidence of bone resorption, repair and remodelling.[102-104]

McCord and Bradley (1989) investigated the effect of two ceramic materials, dense hydroxyapatite and beta tricalcium phosphate, implanted over cryosurgically treated mandibles of rats at a subperiosteal level. Not only were the results of Fisher et al 1977 confirmed, but both of these materials were found to prevent the loss of strength due to cryosurgery.[116]

Malawer et al (1988) demonstrated in an experiment using dogs, that cryosurgery can produce bone necrosis 7 to 12 millimeter away from the surface of the cavity being treated, in contrast to the minimal zone of necrosis produced by the heat of polymerization of polymethyl-methacrylate. In contrast to earlier studies,[111-113] he found that cryosurgery had no effect on articular cartilage.[117]

Yun et al (1993) compared the effect of cryosurgery, phenol cautery and packing with bone cement in terms of bone necrosis and subsequent healing of surgical defects in the dog femur. The authors demonstrated that cryosurgery produced necrosis between 2.5 and 14 mm away from the lesion. The heating effect of bone cement produced necrosis at a depth of 1.3 to 2.8 mm. Phenol produced negligible necrosis away from the surface of the bone being treated. Complete regeneration in the region of necrosis after cryosurgery was observed by 24 weeks. The authors concluded that cryosurgery could play a significant role as a surgical adjunct to curettage in locally aggressive benign tumors and in some malignancies. Packing with cement was felt to be useful only in benign cases. Phenol cautery was not regarded as an adequate treatment after curettage of bone tumors.[118]

Oeseburg (1977) published a thesis called "Cryosurgical treatment of some bonetumors, an experimental and clinical investigation". He performed a cryosurgical "en block" lesion in the forleg of 55 rabbits, which was investigated at fixed intervals after the freeze. Radiographical and histological examination showed a partial repair after 4 weeks and a complete repair of the "en block" frozen tissues after 8 weeks, with the exception of cartilage.[119]
De Vries (1983) conducted experiments in rats and rabbits to evaluate the problem of bonemarrow embolism during cryosurgery. It was concluded that the intravasation of bone marrow was caused by increased intramedullary pressures and embolization of bone marrow was encountered, but not on a large scale. Most of the bonemarrow intravasations remained locally in the extraosseous veins[120].

CLINICAL DATA ON CRYOSURGERY OF BONE

The first cryosurgical treatment for musculoskeletal disease was performed in the early nineteen sixties. *Marcove et al (1968 and 1969)* in New York, USA introduced the technique in 1964 for the treatment of pain caused by bony metastases that had failed to respond to radiation therapy. Encouraging initial clinical results, laboratory research and technical improvements resulted in expansion of the indication for cryosurgery to primary benign bone tumors such as aneurysmal bone cysts and giant cell tumors as well as low-grade malignant bone tumors such as chondrosarcoma. Local recurrence rates with this treatment were found to be low and early morbidity declined with experience.[121-123] These three papers of Marcove, although in different journals, but with the same message and material were the first of a long series concerning the use of cryosurgery in musculoskeletal oncology by this author.
Gage et al (1968), New York, USA, was less enthusiastic about his early experience with the cryosurgical treatment of bone: "In general we have been disappointed with the results obtained in the treatment of bone tumors. Early impressions of benefit from favorable response after freezing have been altered by sobering evidence of persistent tumor". But Gage had confidence in the future based on his favorable experience with soft tissue tumors: "It is likely that better results will follow improvements in technique".[124]
After first publishing the results of 25 patients with giant cell tumor,[125] *Marcove et al (1978)* added a second series of 27 patients all treated with cryosurgery. The improvement in technique was the direct pouring of liquid nitrogen into the curetted cavity, which gave a reliable filling and freezing of the irregular walled cavity. To detect local recurrences almost all cases were subjected to "second look biopsy". Although clinically inapparent and not detectable on radiographs, microscopic examination of these biopsies revealed 9 patients with residual tumor among the first 25 patients. In the second series 3 patients had viable tumor. Complications of cryosurgery, particularly fractures, decreased sharply to

acceptable levels in the second series of patients. All neuropraxias following cryosurgery resolved almost completely.[126]

Marcove et al (1977) reported on the treatment of 18 patients with grade 1 and 2 chondrosarcoma with curettage and cryosurgery. Soft tissue masses were frozen as well. 12 Patients required further operative treatment for microscopic recurrence as shown by second look biopsy (6 patients) and/or postcryosurgical fractures (6 patients). Transient nerve palsies were seen in 4 patients. Seven patients ultimately required en bloc resection or ablative surgery necessitating massive reconstructive procedures, and compromising the initial goal of cryosurgery, which was to avoid the loss of bone stock. However, after 66 months of follow-up all but one of the patients was free of disease.[127]

Marcove et al (1977) used cryosurgery in combination with internal fixation for the treatment of pathological fractures due to metastases from renal cell carcinoma. He reported good local control and disease palliation.[128]

Marcove's initial successes with cryosurgery for bone tumors resulted in more widespread usage of the technique.

Oeseburg et al (1978) from the Netherlands reported five cases of aneurysmal bone cyst treated with curettage and cryosurgery to extend the surgical margin without further loss of bone. Bone grafts were used to fill the cavity. After a mean follow-up of 35 months no recurrences were seen.[129]

Popescu and Spirescu (1980) from Romania treated four mandibular tumors with mandibular hemiresection, extracorporal cryosurgery and immediate reimplantation, a technique based on the experimental work.[130,131] One case had almost 100% and another partial incorporation of the treated bone. Two failed treatment because of infection.[132]

Mirra et al (1981), Los Angeles, USA, reported on the successful treatment of a low-grade neoplastic giant-cell tumor of the C_2 vertebral body with a combination of cryosurgery and radiotherapy. The entire body of C_2 was deeply frozen. The spinal fluid proved to be an effective barrier in preventing freeze injuries of the spinal cord. Fifty-three months after operation there was no evidence of recurrence and the vertebral body was completely remodelled.[133]

In a review article *Marcove (1982)* described his long term experience with cryosurgery for malignant lesions, which had been published separately.[123,127,128] He also provided further results of this treatment for benign bonetumors. He added 50 patients with giant cell tumor to his previous 52 patients[125,126] and found a local recurrence rate of only 2%. Twenty-three patients with unicameral bone cysts and 33 patients with aneurysmal bone cysts each had two local recurrences. In 18 patients with chondroblastoma there were three local recurrences. Four patients with fibromyxoma of bone, seven with fibrous dysplasia and four with eosinophilic granuloma all had no local recurrences.[134]

The primary cryosurgical treatment of three patients with osteosarcoma was first performed by *Marcove et al (1984)*. Second-look biopsy revealed no residual tumor. One patient needed an above knee amputation because of infection and a second underwent multiple wedge resections of lung metastases. The three patients were free of disease at six, nine and 38 months after initial treatment.[135]

Gartsman and Ranawat (1984), New York, USA, reported the successful use of cryosurgery as adjuvant treatment after curettage of a recurrent osteoid osteoma of the proximal phalanx.[136]
Russe et al (1984) from Germany treated 27 benign bone tumors of various type with curettage and cryosurgery. He had four local recurrences. He also reported that in 15 patients with malignant metastatic disease, good local control was achieved.[137]
Jacops et al (1985), Milwaukee, USA updated their results of cryosurgery for giant cell tumor published in 1983.[138] Two out of 12 patients had a local recurrence and required further treatment. Five patients suffered six postcryosurgical fractures. After an average follow-up of 51 months all patients were free of disease.[139]
de Vries et al (1986), The Netherlands, treated four chordomas in situ by freezing the tumor. In two patients it was technically possible to freeze the entire tumor through a dorsal approach. They were alive 12 and 7 years after the operation, but one needed self catheterization. One patient died with recurrent disease at five years. One patient was alive with recurrent disease at four years.[140]
Meals et al (1989) Los Angeles, USA successfully treated a giant cell tumor of the metacarpal bone with curettage, cryotherapy and bone grafting. Mild paresthesia complicated the treatment but resolved within six months.[141]
Malawer and Dunham (1991) Washington, USA reviewed 25 pediatric patients with aggressive benign tumors all treated with cryosurgery. The average follow-up period was 60.8 months. The local recurrence rate was 4% and secondary fracture rate 8%. The functional outcome was fair in one patient (4%), good in 13% and excellent in 83%.[142]
Pogrel (1993) San Francisco, USA treated 37 aggressive mandibular lesions (25 keratocyts, 8 ameloblastomas, 2 giant cell tumors and 2 myxomas) with cryosurgery. No recurrences were seen after a mean follow-up of 75 months. [143]
Aboulafia et al (1994) Washington, USA described a technique for treatment of large subchondral tumors around the knee which extended to within two millimeter of the articular surface. Curettage, cryosurgery and composite reconstruction with bone graft, bone cement and osteosynthesis was used as an alternative to primary joint sacrificing resection. Out of nine tumors (six giant cell tumors, one chondroblastoma, one chondrosarcoma and one fibrosarcoma) there was one recurrence, retreated in the same fashion. All 9 patients had an excellent functional outcome. Only two patients had mild degenerative cartilage changes.[144]
Marcove (1994) New York, USA treated four patients with giant cell tumor of the sacrum with curettage and cryosurgery and three with limited excision and cryosurgery. Two had local recurrence and two had positive second look biopsy with microscopic tumor all treated successfully with second cryosurgical procedures.[145]
Salmassy et al (1995) San Francisco, USA reviewed 20 patients with aggressive mandibular lesions treated with curettage and cryosurgery. Ten patients received an additional autogenous bone graft and ten did not. None of the patients with an

additional bone graft suffered a complication. In the non-bone grafting group two pathologic fractures occurred, both in lesions with a diameter larger than 4.0 cm.[146]

CONCLUSIONS

From the above mentioned experimental data it is clear that cryosurgery is by far the most effective method of producing bone necrosis when compared to bone cement and phenol. It is therefore a valuable adjuvant, enabling an extended surgical margin in almost every benign and low-grade malignant skeletal tumor. Acceptable disease control with local recurrence rates of 15% or less can be achieved.

Its use as primary treatment without resection for carefully selected malignant tumors, e.g. chordoma should still be considered experimental.

Experiments in animals showed that the remodelling of frozen bone, resulting in normal strength takes about 3 to 6 months. This observation has been clinically borne out as evidenced by a high postcryosurgical fracture rate in many authors' early reports.

Experience and improvements in technique have reduced the fracture rate to an acceptable level. The rate of other complications such as wound dehiscence and infection compare favorably to other treatments.

Although some experimental evidence suggests that articular cartilage is irreversibly damaged by cryosurgery, this has only been partially substantiated in clinical series.

If nerves are frozen their function is only temporary impaired. Most neuropraxias resulting from freezing will resolve in 6 weeks to 6 months.[147] Very likely regenerating nerve fibers can grow down the nerve sheaths since they are left intact. Furthermore the vital nerve cell nucleus is located away in the dorsal root ganglion.

REFERENCES CHAPTER 2 - 5

1 **Ernst E and Fialka V.** Ice freezes pain? A review of the clinical effectiveness of analgesic col d therapy. J Pain Symptom Manage 1994; 9: 56-9.

2 **Breasted JH.** The Edwin Smith Surgical Papyrus.
Chicago, University of Chicago Oriental Institute Publications Vol III 1930; 1: 217-224.

3 **Zonnevylle JA.** The influence of cryosurgery and electrogoagulation on the process o f metastasizing. Thesis, Oegstgeest, Drukkerij de Kempenaer, 1981; p 13.

4 **Gratton JHG and Singer C.**Anglo-Saxon magic and medicine.
London, Oxford University Press, 1952; p 165.

5 **Davison MHA.** The evolution of anesthesia. Brit J Anaesth 1959; 31: 134.

6 **Bracco D.** Handbook on cryosurgery, Historical developments.
New York, Marcel Dekker, 1980; p 4.

7 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1.
Boca Raton, Florida, CRC Press, 1986; p 2.

8 **Walder HAD.** Toepassing van de bevriezingsmethode in de neurochirurgie. Thesis.
Schriks' drukkerij N.V, Asten, 1966; p 1.

9 **Larrey DJ.** Surgical memoirs of Campaigns of Russia, Germany and France.
Translation by JC Mercer Philadelphia, Carey and Lea, 1832; p 293.

10 **Allen FM.** Refrigeration anaesthesia for limb operations. Anesthesiology 1943; 4: 12-16.

11 **Massie FM.** Refrigeration anesthesia for amputations. Ann Surg 1946; 73: 737-47.

12 **Harbrecht P, Nethery H, Ahmad W et al.** Freezing an extremity in preparation for amputation .
South Med J 1978; 71: 926-29.

13 **Hunsaker R, Schwartz J, Keasy B et al.**Dry ice cryoamputation: a twelve-year experience.
J Vasc Surg 1985; 2: 812-16.

14 **Bunt TJ.** Physiologic Amputation. Preliminary cryoamputation of the gangrenous extremity.
AORN Journal 1991; 54: 1220-4.

15 **Lohr JM, Lutter KS, Johnson JR, Hall CF, Hearn AT, Welling RE and Cranley JJ**Experience with physiologic amputation using the cryocare extremity stabilization system (CESS). J Cardiovas c Surg 1992; 33: 461-3.

16 **Arnott J.** On the present state of therapeutical Inquiry.
Brighton, King, and London, J. Churchill, 1845; p 35.

17 **Arnott J.** On the treatment of cancer by the regulated application of an anaesthetic temperature .
London, J. Churchill 1851.

18 **Richardson BW.** On a new and ready mode of producing local anaesthesia. Med Times an d Gazette 1866; 1: 115.

19 **Samuel S.** Erstarrung und Entzundung. Virchows Arch 1868; 43: 552.

20 **Openchowski P.** Sur l'action localisée du froid, appliqué à la surface de la région cortical d u cerveau. CR Soc Biol (Paris) 1883; 35: 38.

21 **White AC.** Liquid air: its application in medicine and surgery. Med Rec 1899; 56: 109-12.

22 Liquid air in Medicine and Surgery. Scientific American 1899; August 5: p 83.

23 **White AC.** Possibilities of liquid air to the physician. JAMA 1901; 36: 426-28.

24 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1.
Boca Raton, Florida, CRC Press, 1986 p 4.

25 **Whitehouse HH.** Liquid air in dermatology: its indications and limitations.
JAMA 1907; 49: 371-7.

26 **Pusey WA.** The use of carbon dioxide snow in the treatment of nevi and other lesions of the skin .
JAMA 1907; 49: 1354-6.

27 **Gold J.** Liquid air and carbonic acid snow: therapeutic results obtained by dermatologists.
NY Med J 1910; 92: 1276-7.

28 **Irvine H and Turnacliff D.**Liquid oxygen in dermatology.
Arch Dermatol Syphilol 1929; 19: 270-80.

29 **Lortat-Jacobs L and Solente G.**La Cryotherapy. Paris, Masson et Cie, 1930.

30 **Kuflik EG and Gage AA.**Cryosurgical treatment for skin cancer.
New York, Igaku-Shoin, 1990; p 3.

31 **Fay T and Henny GC.** Correlation of body segmental temperature and its relation to the location of carcinomatous metastases: Clinical observations and response to methods of refrigeration. Surg Gynec Obstet 1938; 66: 512-24.

32 **Fay T.** Observations on prolonged human refrigeration. New York J Med 1940; 40: 1351-4.

33 **Cooper IS.** Cryogenic Surgery. A new method of destruction or extirpation of benign or malignant tissues. NEJM 1963; 14: 743-9.

34 Editorial. Cold as a surgical instrument. NEJM 1963; 14: 790.

35 **Maroon JC, Onik G, Quigley MR, Bailes JE, Wilberger JE and Kennerdell JS.** Cryosurgery revisited for the removal and destruction of brain, spinal and orbital tumours. Neurol Res 1992; 14: 294-302.

36 Editorial. Current status of gastric freezing. NEJM 1963; 14: 755-6.

37 **Blair E.** Clinical Hypothermia. New York, McGraw-Hill Book Company, 1964.

38 **Gailletet L.** Annales de chemie et de physique 1878; 15: 113.

39 **Wroblewski SU and Olszewski KS.** Wiedemann's Annalen de Physik 1883; 20: 256.

40 **Poppe J.** The use of cold air blast in precancerous skin lesions and haemangiomas. Surgery 1942; 11: 460-5.

41 **Carpenter CC.** Cryotherapy for common skin diseases. J Med Soc NJ 1943; 40: 354-57.

42 **Allington H.** Liquid nitrogen in the treatment of skin diseases. Calif Med 1950; 72: 153-5.

43 **Kuflik EG.** Cryosurgery updated. J Am Acad Dermatol 1994; 31: 925-44.

44 **Grimmett R.** Liquid nitrogen therapy. Histologic observations. Arch Dermatol 1961; 83: 563-7.

45 **Cooper I and Lee A.** Cryostatic congelation: a system for producing a limited controlled region of cooling or freezing of biologic tissues. J Nerv Ment Dis 1961; 133: 259-63.

46 **Cooper IS.** Cryogenic surgery of the basal ganglia. JAMA 1962; 181: 600-4.

47 **Zacarian S and Adham M.** Cryotherapy of cutaneous malignancy. Cryobiology 1966; 2: 212-8.

48 **Zacarian S and Adham M.** Cryogenic temperature studies of human skin. Temperature recordings at two millimeter human skin depth following application with liquid nitrogen. Cryobiology 1967; 48: 7-10.

49 **Ramming KP.** Cryosurgery: The coming of the surgical ice age. J Surg Oncol 1995; 58: 147-8.

50 **Gage AA.** Cryosurgical Societies: A historical note. Cryobiology 1989; 26: 302-5.

51 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1. Boca Raton, Florida, CRC Press, 1986 chapter 5.

52 **Zacarian S.** Is lateral spread of freeze a valid guide to depth of freeze? J Dermatol Surg Oncol 1978; 4: 561-63.

53 **Cooper I.** Cryogenic surgery for cancer. Fed Proc 1965; 24: 237-40.

54 **Gage A, Caruana J and Garamy G.** A comparison of instrument methods of monitoring freezing in cryosurgery. J Dermatol Surg Oncol 1983; 9: 209-14.

55 **Gill W, DaCosta J and Fraser J.** The control and predictability of a cryolesion. Cryobiology 1970; 6: 347-53.

56 **Zacarian S.** How accurate is temperature monitoring in cryosurgery and is there an alternative? J Dermatol Surg Oncol 1980; 6: 627-32.

57 **Le Pivert P, Binder P and Ougier T.** Measurement of intratissue bioelectrical low frequency impedance: a new method to detect pre-operatively the destructive effect of cryosurgery. Cryobiology 1977; 14; 245-50.

58 **Le Pivert P.** The measurement of low frequency electrical impedance as a guide to effective cryosurgery. J Dermatol Surg Oncol 1977; 3: 395-7.

59 **Gage AA, Augustynowicz S, Montes Met al.** Tissue impedance and temperature measurements in relation to necrosis in experimental cryosurgery. Cryobiology 1985; 22: 282-8.

60 **Gage A.** Correlation of electrical impedance and temperature in tissue during freezing. Cryobiology 1979; 16: 56-62.

61 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1. Boca Raton, Florida, CRC Press, 1986 p 130-2.

62 **Bradley PF and Fisher AD.** The cryosurgery of bone, an experimental and clinical assessment. Br J Oral Surg 1975; 13: 111-27.

63 **Ravikumar T, Kane R, Cady B et al.** Hepatic cryosurgery with intraoperative ultrasound monitoring for metastatic colon carcinoma. Arch Surg 1987; 403-9.
64 **Laugier P and Berger G.** Assessment of echography as a monitoring technique for cryosurgery. Ultrasonic Imaging 1993; 15: 14-24.
65 **Moser R, Abbott I, Stephens C et al.** Computerized tomographic imaging of cryosurgical iceballformation in brain. Cryobiology 1987; 24 368-79.
66 **Pease GR, Rubinsky B, Wong STS, Roos MS, Gilbert JC and Arav A** An integrated probe for magnetic resonance imaging monitored skin cryosurgery.
J Biomech Eng 1995; 117: 59-63.
67 **Hong JS, Wong S, Pease G and Rubinsky B.** MR imaging assisted temperature calculations during cryosurgery. Magnetic Resonance Imaging 1994; 12: 1021-31.
68 **Matsumoto R, Selig AM, Colucci VM and Jolsz FA.** MR monitoring during cryotherapy in the liver: predictability of histologic outcome. JMRI 1993; 3: 770-6.
69 **Richardson ML, Lough LR, Shuman WP, Lazerte GD and Conrad EU.** MR appearance of skeletal neoplasms following cryotherapy. Skeletal Radiol 1994; 23: 121-5.
70 **Angell CA and Sare EJ.** Vitreous water; identification and characteristics. Science 1970; 168.
71 **Walton AG.** Nucleation of crystals from solution. Science 1965; 148: 601.
72 **Dowell LG, Rinfrit AP.** Low temperature forms of ice as studied by X-ray diffraction.
Nature 1960; 188: 1144.
73 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1. Boca Raton, Florida, CRC Press, 1986 p 19.
74 **Lovelock JE.** The haemolysis of human red blood cells by freezing and thawing.
Biochim Biophys Acta 1953; 10: 414.
75 **Bischof J, Christov K and Rubinsky.** A morphological study of cooling rate response in normal and neoplastic human liver tissue: cryosurgical implications.
Cryobiology 1993; 30: 482-92.
76 **Shlafer M and Karow AM.** Ultrastructure function correlative studies for cardiac cryopreservation. II. Hearts frozen to various temperatures without a cryoprotectant.
Cryobiology 1971; 8: 350.
77 **Fishbein WN and Stowell RE.** Studies on the mechanism of freezing damage to mouse liver using a mitochondrial enzyme assay. I. Temporal localization of the injury phase during slow freezing. Cryobiology 1968; 4: 283.
78 **McGann L, Yang H and Walterson M.** Manifestations of cell damage after freezing and thawing. Cryobiology 1976; 13: 599-608.
79 **Smith JJ, Fraser J and MacIver AG.** Ultrastructure after cryosurgery of rat liver.
Cryobiology 1978; 15: 426-432.
80 **Fujikawa S.** Freeze-fracture and Etching studies on membrane damage on human erythrocytes caused by formation of intracellular ice. Cryobiology 1980; 17: 351-62.
81 **Quinn PJ.** A lipid-phase separation model of low-temperature damage to biological membranes. Cryobiology 1985; 22: 128-46.
82 **Bank H.** Visualization of freezing damage. II. Structural alterations during warming.
Cryobiology 1973; 10: 157.
83 **Miller RH and Mazur P.** Survival of frozen-thawed human red cells as a function of cooling and warming velocities. Cryobiology 1976; 13: 404-
84 **Raab JM, Renaud ML, Brandt PA et al.** Effect of freezing and thawing on the microcirculation and capillary endothelium of the hamster cheek pouch.
Cryobiology 1974; 11: 508-18.
85 **Rothenborg HW.** Cutaneous circulation in rabbits and humans before, during and after cryosurgical procedures measured by Xenon-133 clearance. Cryobiology 1970; 6: 507-11.
86 **Bradley PF.** Cryosurgery of the maxillofacial region, Vol 1.
Boca Raton, Florida, CRC Press, 1986 p 23.
87 **Kuylenstierna R, Lundquist PG and Nathanson A.** Early morphological changes in rabbit mandible after cryogenic application. Arch Otorhinolaryngol 1980; 226: 35-43.
88 **Gill W, Frazer J and Carter D.** Repeated freeze-thaw cycles in cryosurgery.
Nature 1968; 219: 410-13.
89 **Gage A.** Experimental cryogenic injury of the palate: observations pertinent to cryosurgical destruction of tumors. Cryobiology 1978; 15: 415-25.

90 **Neel HB, Ketcham AS and Hammond WG.** Requisites for successful cryogenic surgery o f cancer. Arch Surg 1971; 102: 45.

91 **Berth-Jones J, Bourke J, Eglitis H, Harper C, Kirk P, Pavord S, Rajapakse R, Weston P Wiggins T and Hutchinson PE.** Value of a second freeze-thaw cycle in cryotherapy of commo n warts. Br J Dermatol 1994; 131: 883-6.

92 **Kreyberg L.** Tissue damage due to cold. Lancet 1946; 1: 338-40.

93 **Holden HB and McKelvie P.** Cryosurgery in the treatment of head and neck neoplasia. Br J Surg 1972; 59: 709-12.

94 **Zacarian S, Stone D and Clater M.** Effects of cryogenic temperatures on the microcirculation i n the golden hamster cheek pouch. Cryobiology 1970; 7: 27-39.

95 **Zacarian SA.** The observation of freeze-thaw cycles upon cancer-cell suspensions. J Dermatol Surg Oncol 1977; 3: 173-4.

96 **Marcove RC, Sadrieh J, Huvos AG and Grabstald H.** Cryosurgery in the treatment of solitary o r multiple bone metastases from renal cell carcinoma. J Urol 1972; 108: 540-7.

97 **Gage A.** Cryosurgery for difficult problems in cutaneous cancer. Cutis 1975; 16: 465-70.

98 **Kuylenstierna R and Lundquist PG.** Bone destruction by direct cryoapplication: a temperatur e study in rabbits. Cryobiology 1982; 19: 231-36.

99 **Gage AA.** What temperature is lethal for cells? J Dermatol Surg Oncol 1979; 5: 459-60.

100 **Gage AA, Caruana JA and Montes M.** Critical temperature for skin necrosis in experimenta l cryosurgery. Cryobiology 1982; 19: 273-

101 **Gage AA, Guest K, Montes M, Caruana JA and Whalen Jr DA.** Effect of varying freezing an d thawing rates in experimental cryosurgery. Cryobiology 1985; 22: 175-82.

102 **Gage AA and Emmings FG.** Bone freezing in cryotherapy. J Barnabus Med Center 1967; 4: 314-19.

103 **Hausamen JE.** Tierexperimentelle Untersuchungen zur Knochendestruktion und Regeneration a m Kaninchenkiefer nach kryochirurgischer Behandlung. Dtsch Zahnärztl Z 1973; 28: 836-43.

104 **Schargus G, Winckler J, Schröder F and Schäfer B.** Cryosurgical devitalization of bone and it s regeneration. An experimental study with animals. J Maxillofac Surg 1975; 3: 128-31.

105 **Gage AA, Greene GW, Neiders ME and Emmings FG.** Freezing bone without excision. A n experimental study of bone-cell destruction and manner of regrowth in dogs. JAMA 1966; 196: 90-4.

106 **Marcove RC.** Cryogenics in surgery. New York, Medical Examination Publishing Company Inc 1971; p 397-410.

107 **Kuylenstierna R, Lundquist PG and Nathanson A.** Destruction and regeneration of jawbon e after cryogenic application. An experimental study. Ann Otol 1980; 89: 582-9.

108 **Kuylenstierna R, Nathanon A and Lundquist PG.** Effects of cryosurgery on the healing patter n of rabbit mandibular bone. A triple fluorochrome labelling study. Acta Otolaryngol 1981; 92: 569-74.

109 **Kerschbaumer F, Russe W, Weiser G and Bauer R.** Cryolesions of bone. An experimental study. Part I: Examinations in technique of controlled cryolesion on bone. Arch Orthop Traumat Surg 1980; 96: 5-9.

110 **Kerschbaumer F, Russe W and Bauer R.** Grundlagen der Kryochirurgie in der Orthopädie. Orthopäde 1984; 13: 133-41.

111 **Marciani RD, White DK and Roth GI.** Freeze treatment of the monkey mandibular condyle. J Oral Maxillofac Surg 1986; 44: 50-9.

112 **Lenz H and Preussler H.** Wirkung des Kryoeffektes auf den wachsenden Knochen . Morphologische Veränderungen am Beispiel des Kniegelenkes vom Kaninchen. Laryngol Rhinol Otol Stuttg 1975; 54: 317-27.

113 **Schneider UA.** Experimentelle Untersuchungen des Wachstumsverhaltens von Röhrenknoche n nach Kältebehandlung im Epiphysenbereich. Orthopäde 1981; 10: 13-8.

114 **Müller LCh, Micksche M, Yamagata S and Kerschbaumer F.** Therapeutic effect of cryosurger y of murine osteosarcoma. Influence on disease outcome and immune function. Cryobiology 1985; 22: 77-85.

115 **Fisher AD, Williams DF and Bradley PF.** The effect of cryosurgery on the strength of bone. Br J Oral Surg 1978; 15: 215-22.

116 **Mc Cord JF and Bradley PF.** Observations on the effect of two ceramics on the strength of bon e subjected to cryosurgery. Br J Oral Maxillofac Surg 1989; 27: 217-23.

117 **Malawer MM, Marks MR, McChesney D, Piasio M, Gunther SF and Schmookler BM.** The effect of cryosurgery and polymethylmethacrylate in dogs with experimental bone defects comparable to tumor defects. Clin Orthop 1988; 226: 299-310.
118 **Yun YH, Kim NH, Han DY and Kang ES.** An investigation of bone necrosis and healing after cryosurgery, phenol cautery or packing with bone cement of defects in the dog femur. Int Orthop 1993; 17: 176-83.
119 **Oeseburg HB.** Cryosurgical treatment of some bone tumors, an experimental and clinical investigation. Thesis, Groningen, 1977.
120 **de Vries J.** Bonemarrow embolism and cryosurgery. Thesis, Groningen, 1983.
121 **Marcove RC and Miller TR and Cahan WC.** Treatment of primary and metastatic bone tumors by repetitive freezing. Bull N Y Acad Med 1968, 44: 532-44.
122 **Marcove RC and Miller TR.** Treatment of primary and metastatic bone tumors by cryosurgery. JAMA 1969; 207: 1890-4.
123 **Marcove RC and Miller TR.** The treatment of primary and metastatic localized bone tumors by cryosurgery. Surg Clin North America 1969; 49: 421-30.
124 **Gage AA and Erickson RB.** Cryotherapy and curettage for bone tumors. J Cryosurgery 1968; 1: 60-66.
125 **Marcove RC, Lyden JP, Huvos AG and Bullough PG.** Giant cell tumors treated by cryosurgery. J Bone Joint Surg 1973; 55: 1633-44
126 **Marcove RC, Weis LD, Vaghaiwalla MR, Pearson R.** Cryosurgery in the treatment of giant cell tumors of bone. A report of 52 consecutive cases. Clin Orthop 1978; 134: 275-89.
127 **Marcove RC, Stovell PB, Huvos AG and Bullough PG.** The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. A preliminary report. Clin Orthop 1977; 122: 147-56.
128 **Marcove RC, Searfoss RC, Whitmore WF and Grabstald H.** Cryosurgery in the treatment of bone metastases from renal cell carcinoma. Clin Orthop 1977; 127: 220-7.
129 **Oeseburg HB, Rogge CWL, Schraffordt Koops H, Oldhoff J.** Cryosurgical treatment of aneurysmal bone cysts. J Surg Oncol 1978; 10: 9-20.
130 **Marciani RD and Bowden CM.** Reimplantation of freeze-treated mandibular bone. J Oral Surg 1975; 33: 261.
131 **Marciani RD and Giansanti JC.** Reimplantation of freeze-treated and saline-treated mandibular bone. J Oral Surg 1976; 34: 314.
132 **Popescu V and Spirescu IE.** Bone resection, extra-corporal cryotherapy and immediate reimplantation in the treatment of mandibular tumours. J Maxillofac Surg 1980; 8: 8-16.
133 **Mirra JM, Rand F, Rand R, Calcaterra T and Dawson E.** Giant-cell tumor of the second cervical vertebra treated by cryosurgery and irradiation. Clin Orthop 1981; 154: 228-33.
134 **Marcove RC.** A 17-year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1982; 163: 231-4.
135 **Marcove RC, Zahr KA, Huvos AG and Ogihara W.** Cryosurgery in osteogenic sarcoma: a report of three cases. Comprehensive Therapy 1984; 10: 52-60.
136 **Gartsman GM and Ranawat CS.** Treatment of osteoid osteoma of the proximal phalanx by the use cryosurgery. J Hand Surg 1984; 9: 275-7.
137 **Russe W, Kerschbaumer F and Bauer R.** Kryochirurgie in der Orthopädie. Orthopäde 1984; 13: 142-50.
138 **Jacobs PA and Clemency RE.** The closed cryosurgical treatment of giant cell tumor, aneurysmal bone cyst and other lesions of bone. Orthop Trans 1983; 7: 196-
139 **Jacobs PA and Clemency Jr RE.** The closed cryosurgical treatment of giant cell tumor. Clin Orthop 1985; 192: 149-58.
140 **Vries de J, Oldhoff J and Hadders HN.** Cryosurgical treatment of sacrococcygeal chordoma. Report of four cases. Cancer 1986; 58: 2348-54.
141 **Meals RA, Mirra JM and Bernstein AJ.** Giant cell tumor of metacarpal treated by cryosurgery. J Hand Surg 1989; 14: 130-4.
142 **Malawer MM and Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors. Analysis of 25 patients below the age of 21. Clin Orthop 1991; 262: 42-57.
143 **Pogrel MA.** The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. J Oral Maxillofac Surg 1993; 51: 269-73.

144 **Aboulafia AJ, Rosenbaum DH,Sicard-Rosenbaum L, Jelinek JS and Malawer MM.**Treatment of large subchondral tumors of the knee with cryosurgery and composite reconstruction. Clin Orthop 1994; 307: 189-99.

145 **Marcove RC, Sheth DS, Brien EW, Huvos AG and Healey JH.**Conservative surgery for gian t cell tumor of the sacrum. Cancer 1994; 74: 1253-60.

146 **Salmassy DA and Pogrel MA.** Liquid nitrogen cryosurgery and immediate bone grafting in th e management of aggrassive primary jaw lesions. J Oral Maxillofac Surg 1995; 53: 784-90.

147 **Heidenheim M and Jemec GBE.**Side effects of cryotherapy.
J Am Acad Dermatol 1991; 24: 653.

CHAPTER 6

THE TREATMENT OF SIMPLE BONE CYSTS IN CHILDREN WITH CURETTAGE AND CRYOSURGERY*

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ABSTRACT

A retrospective study in children with simple or unicameral bone cysts treated with curettage, cryosurgery and bone grafting was conducted. The purpose of this study was to evaluate local tumor control and bony healing following this method of treatment. Five of 42 (12%) treated patients suffered a local recurrence with a mean clinical follow-up of 24.5 months. Surgical complications consisted of two superficial wound infections, one radial nerve palsy and two fractures which all resolved completely.
A review of the literature was performed to compare our results to historical controls utilizing steroid injection therapy and curettage with bone grafting alone.
We believe that the use of cryosurgery as adjuvant therapy in the surgical treatment of simple bone cysts is of value in controlling local recurrences and achieving bony consolidation.

INTRODUCTION

Simple bone cyst is a tumor of bone of unknown origin. It tends to occur in the metaphyses of long bones, particularly of the humerus and femur. Although histological completely benign, it frequently weakens the integrity of bone resulting in pathological fracture, which is often the presenting feature. The treatment options for simple bone cysts (SBC) include observation, injection and surgical curettage. Until Scaglietti et al introduced the technique of steroid injections,[1,2] the most prevalent treatment method for SBC has been curettage followed by bone grafting with recurrent rates that vary from 12 to 48%.[3-12] Adjuvant therapy after curettage has been advocated to destroy residual tumor cells and lower tumor recurrence. In theory adjuvant treatments include

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radiotherapy, cytotoxic physicals like phenol and hypertonic saline, merthiolate, cement and cryosurgery. The purpose of this study is to evaluate local tumor control and bony healing following the treatment of simple bone cysts with curettage, cryosurgery and allograft bone grafting. A review of the literature is included and our results are compared to historical controls.

MATERIALS AND METHODS

A retrospective study of all patients with a simple bone cyst treated in our institution was carried out including a review of all patient records, radiographs and pathology reports. The diagnosis of a simple bone cysts was made when membranous tissue was found within the cyst or when the cyst was found to contain no tissue at all. The cysts may or may not have contained serous or serosanguineous fluid. Cysts containing tissue consistent with aneurysmal bone cyst were excluded. Fiftythree patients were subsequently diagnosed with simple bone cyst and treated with curettage, cryosurgery and bone grafting between 1989 and 1996. Eleven patients were treated in 1995 and excluded for follow-up of less than 12 months, leaving 42 patients in this study.

The following clinical parameters were assessed for each patient: age, sex, history and previous treatment, anatomic location, pathology results, postoperative complications and function and length of follow-up. Radiographs were reviewed in order to determine anatomic location, presence of pathological fracture, cyst size (greatest diameter), postoperative osseous healing and the presence of local recurrence. Staging was accomplished using the radiographic criteria for benign lesions of bone defined by Enneking.[13]

The operative treatment of SBC in our patient group consisted of intralesional curettage via bony fenestration followed by cryotherapy and bone grafting. Cryotherapy or cryosurgery was performed using an apparatus (Kryospray^{R}II, Brymill Corporation, Vernon CT, USA) producing a liquid nitrogen spray by which the osseous cavity was frozen and then thawed using a warm saline solution. Three cycles of freezing and thawing were carried out after a limited curettage executed by curettes and a mechanical burr. The bony defect was then filled with allogenic freeze dried bone chips, which were procured and processed according to guidelines recommended by the American Association of Tissue Banks.[14] Care was taken not to damage the adjacent physis by curettage and if the physis was exposed to the cyst, it was separated from freezing by several layers of surgical gelfoam. When possible, tourniquets were used. For all lower extremity lesions, postoperative full weightbearing was not allowed for approximately 6-12 weeks. Follow-up was achieved by clinical examination and routine radiographs at 1-2 month intervals until bony healing. The results of our treatment were evaluated radiographically using the following classification terminology, modified from a system previously utilized by Neer et al[3,10]:

A. **complete response:** the space occupied by the cyst is completely filled with new bone formation with remodelling or consolidation of the bone graft.

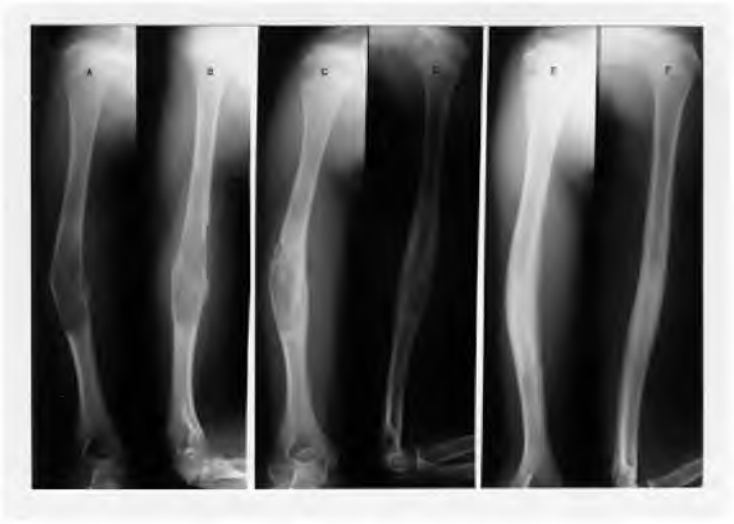

Figure 6.1: Simple Bone Cyst of the humerus in an 11 year old girl. Preoperative radiographs showing pathological fracture (A,B). Postoperative radiographs at two months after curettage, cryosurgery and bone grafting (C,D), and at 13 months demonstrating complete consolidation of the grafted site and humeral remodelling (E,F).

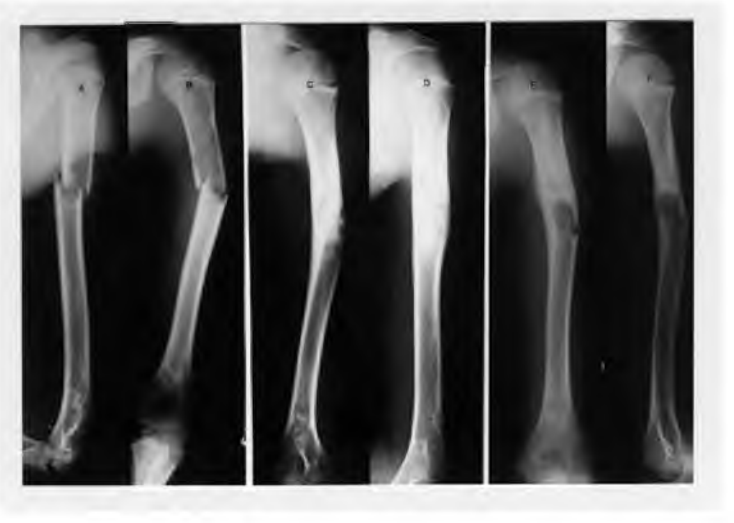

Figure 6.2: Simple Bone Cyst of the humerus in a 12 year old boy. Preoperative radiographs showing displaced pathologic fracture (A,B). Postoperative radiographs at two months showing a small early recurrence at the lateral cortex (C,D), and at four months showing progression of the local recurrence, which was subsequently treated (E,F).

B. **partial response:** small areas (<1.0 cm) of radiographic lucencies are seen within the boundaries of the previous cyst which otherwise demonstrates complete bone formation and remodelling of the graft. With continued radiographic follow-up no increase in size of these lucencies are recognized over time.
C. **local recurrence:** radiographic lucency, within or adjacent to the prior cyst that enlarges radiographically over time.
D. **no response:** no radiographic evidence of bony healing following injection. This response is applicable only to patients who have been treated with steroid injection(s).

The treatment results of the historical controls collected from the literature were also reviewed and scored using this classification system. Statistical significance to identify patient related factors affecting recurrence was determinated by using chi-square analysis.

RESULTS

Our patient group consisted of 31 (74%) males and 11 (26%) females. Eighteen (43%) patients were younger than 11 years of age and 24 (57%) were between 11 and 20 years of age (Table 6.1). The mean age at which the first operation was performed using cryosurgery was 11 years (range 3-18). The anatomical distribution of the affected sites in our and published series is listed in Table 6.2. In our series the humerus accounted for 71% of the cases. Previous treatment had been carried out in 16 (38%) patients involving one or more injections with steroids in 11 (26%) patients, curettage with bone grafting in 4 (10%) patients and one (2%) patient had received both treatments. Pain was the presenting factor in six (14%) patients and a pathological fracture in 33 (79%) patients, with multiple fractures in eight of those 33 patients. Patients with fractures all had radiographic signs of cortical thinning and endosteal erosion and were all staged according to Enneking's criteria as active benign tumors.[13] The mean longitudinal length of cyst in long bones was 6.2 centimeters (range 1-13). The mean clinical follow-up was 24.5 months (range: 13-64). A "complete response" to treatment (Figure 6.1) was observed in 21 (50%) patients and a "partial response" in 16 (38%) patients. Five (12%) patients suffered a local recurrence (Figure 6.2) and were subsequently further treated as summarized in Table 6.4. All patients, except one were controlled with a second similar surgical treatment. Postoperative complications included two superficial wound infections involving serous wound drainage, which resolved within ten days with oral antibiotics. One patient with a humeral diaphyseal SBC suffered a transient partial radial nerve palsy postoperatively which resolved over six weeks without deficit. Two patients suffered nondisplaced postoperative fractures, that occurred following accidents. Both fractures healed with conservative treatment. Limb length discrepancies of more than two centimeters were not observed. All patients, including those who had successful treatment of local recurrence had excellent function of the treated

limb recorded during their follow-up exams. No specific patient-cyst characteristics (age, gender, size, previous treatment and pathological fracture) could be identified as significant risk factor for a local recurrence, when evaluated by chi-square analysis ($P<0.05$).

Author, reference #	N	male	female	age				pathologic fracture (%)
				0-10	11-20	21-30	>30	
Campanacci, 3	416	295	121	54	312	42	8	45
Inoue, 6	23	15	8	7	11	2	3	22
Oppenheim, 7	53	43	10	74% between 5 and 15 years *				83
Spence, 8	144	103	41	94% < 19 years *				> 50% *
Spence, 9	177	134	43	124	49	3	1	-
Neer, 10	175	120	55	-	-	-	-	fem: 100% hum: 87%
Bovill, 4	32	17	15	70% between 5-15 years *				75
Mylle, 11	59	37	22	mean 15 years *				36
Morton, 12	76	51	25	37	24	6	9	58
Scalietti, 1	163	111	52	> 16 months and < 17 years *				45
Pentimalli, 15	40	26	14	17	23	-	-	95
Schreuder	42	31	11	18	24	-	-	79
Total # patients:	1400	983	417	259	443	53	21	
Percentages of totals:		**70%**	**30%**	**33%**	**57%**	**7%**	**3%**	**66%**

Table 6.1: Data accrued from the literature review of 1400 patients with a diagnosis of simple bone cyst or an equivalent diagnosis (* data not used in totals).

DISCUSSION

The diagnosis of simple bone cyst (SBC) or unicameral bone cyst (UBC) was first described as a specific entity by Virchow in 1876.[8] Typically it refers to a membrane-lined cyst, often filled with clear or serosanguinous fluid of low viscosity. Many cysts do have trabecular loculations, making the term multiloculated cyst also applicable to many cysts. Radiographically a SBC is a central, lucent lesion located in the metaphysis or at the junction of the metaphysis and diaphysis. In younger children it may be located directly adjacent

to the physis. The cyst frequently produces endosteal cortical erosion and is not often associated with some limited expansion of the bony diameter. This expansion makes its radiographic distinction from an aneurysmal bone cyst difficult.

Author, reference #	N	proximal metaphysis humerus	diaphysis humerus	femur	tibia	fibula	cal-caneus	other
Campanacci, 3	416	198	79	116	7	2	5	9
Inoue, 6	23	8	4	3	1	-	1	6
Oppenheim, 7	53	32	-	14	4	1	-	2
Spence, 8	144	77	-	38	12	1	5	11
Spence, 9	177	101	-	47	6	3	9	11
Neer, 10	175	94	-	31	20	4	5	21
Bovill, 4	32	17	14	-	-	-	-	1
Mylle, 11	59	22	-	19	1	2	5	10
Morton, 12	76	25	8	22	-	-	-	21
Scalietti, 1	163	68	23	40	7	5	7	3
Pentimalli, 5	40	16	11	9	3	1	-	-
Schreuder	42	11	19	1	3	2	4	2
Total:	1400	669	144	354	64	21	41	107
Percentages of totals:		**47%**	**10%**	**25%**	**5%**	**2%**	**3%**	**8%**

Table 6.2: Anatomical distribution of simple bone cysts. The result of data accrued from literature review.

Histologically, the cyst is lined by a soft tissue membrane with proliferating fibroblasts and occasional giant cells. SBC has been proposed to be a posttraumatic lesion resulting from the failure of absorption of an intra-osseous hematoma.[15] Others believe the cyst represents the inability of the interstitial fluid to escape from the bone due to blockage in the venous drainage system[16,17] and treatment have been directed toward decreasing the intra-osseous pressure.[18,19] Mirra et al believes that the cysts represent an interosseous synovial cyst, based on electron microscopic analysis of cyst membranes.[20] High levels of oxygen scavengers have been isolated in SBC fluid and implicated in the associated bone destruction.[21]

The demographic characteristics of our series do not differ significantly from the typical picture demonstrated in the literature for SBC. The majority (57%) of patients in the literature with SBC are between the ages of 11 and 20 years, 33% are younger than 11 years old and 10% involves patients older than 20 years (Table 6.1). There is a clear male predominance: 70% against 30% females (Table 6.1). Fiftyseven percent of the cysts are located in the humerus and 25% in the femur. SBC frequently presents with a pathological fracture (68%), often due to a minimal trauma (Table 6.1). Pain without radiographic evidence of fracture is the second most common presentation, while the rest are discovered incidently. When a fracture is present, normal fracture healing will occur and in a small percentage of cases the SBC may heal, however most SBC's will recur without treatment and are at risk for a second fracture.[16,22] Our series of patients with SBC was exceptional only in the relatively high number of humeral cysts and a slightly higher fracture incidence.

Treatment alternatives for SBC in the past have most commonly included steroid injection or operative curettage. Because recurrences following curettage alone remain significant, several forms of local adjuvant treatment have been tried. Phenol as an adjuvant treatment after intralesional curettage of SBC has been reported with a recurrence rate of 20%.[10,23,24] Cementation, or the use of cement is another form of adjuvant treatment utilized in the past for giant cell tumor.[25,26] To our knowledge no data is available on its use as an adjuvant for SBC. Marcove used cryosurgery as adjuvant treatment in 23 patients with a SBC and recorded 2 (9%) recurrences.[27]

We have summarized the published results of the treatment of SBC in Table 6.3. As reasonably possible, the literature treatment results has been classified into A,B,C and D categories as has our own series. The distinction between a "complete response" (A) and a "partial response" (B) is subject to potential intra- and interobserver bias. The categories of "local recurrence" (C) and "no response" (D) represent patients requiring further treatment. As described by this review of the literature, curettage with bone grafting for SBC is associated with an overall mean recurrence rate of 29% (range 12-48%). Using cryosurgery as local adjuvant therapy we have been able to achieve a recurrence rate of 12% (5 out of 42 patients).

Scaglietti et al introduced the technique of steroid injection, which remains widely employed.[1] In his initial series, 76% of the patients failed to respond after the first injection and required more injections. On the average, three to four injections over a period of 12 to 20 months were needed to achieve complete healing in 55% with "rare recurrences" and partial healing in 45% associated with a higher recurrence rate.[1,2] Other series have reported local recurrence together with no response following injection as high as 25%.[3,4] The disadvantage of steroid injections include the need for repeated injections and multiple visits for follow-up over long periods of time. Its ability to produce a completely healed bony defect remains poorly defined. The advantage of injections is the minor extent of the treatment and its minimal associated morbidity.

Cryosurgery using liquid nitrogen has been utilized in orthopaedic oncology for the treatment of benign active and aggressive tumors.[27,28]

Author reference #:	treatment and result respectively recurrence									follow-up y=year m=month	comments
	steroid injection					curettage ± bonegraft					
	N	A	B	C	D	N	A	B	C		
Campanacci, 3	141	71	36	21	13	178	83	38	57	1-35 y	multiple inj.
Inoue, 6	-	-	-	-	-	23	18	2	3	15-39 m	graft: hydroxy-apatite cubes
Oppenheim, 7	18	15	2	1	-	33	20	1	12	6 m - 12 y	50% > 1 inj.
Spence, 8	-	-	-	-	-	144	98	10	36	12 - 48 m	crushed *cortical-bone* allograft
Spence, 9	-	-	-	-	-	177	97	16	64	7 - 156 m	*cancellous-bone* allograft
Neer, 10	-	-	-	-	-	133	80	20	33	> 24 m	40% with zinc chloride/phenol
Bovill, 4	12	6	3	1	2	15	5	3	7	mean 5.6 y	42% > 1 inj.
Mylle, 11	20	5	13	1	1	21	5	6	10	mean 8.5 y	in curet. group: 2 hydroxyapat.
Morton, 12	-	-	-	-	-	58	52*	-	6	27% < 1 y	13 no graft, 29 allo, 16 autograft
Scalietti, 1	163	90+	73+	-	-	-	-	-	-	> 3 y	3-4 inj. 12-20m
Pentimalli, 5	20	14	5	1	-	20	5	12	3	14.9 y	1-5 inj, allo- and autografts
Total:	374	201	132	25	16	802	463	108	231		
Percentages:		**54%**	**35%**	**7%**	**4%**		**58%**	**13%**	**29%**		

Table 6.3: Treatment results from published series. In reviewing these articles we have utilized our modification of the original Neer classification of treatment results (A,B,C and D; see text) for simple bone cysts. The definition has been applied consistently to patients treated with steroid injection or curettage (* = not specified in A or B, + = recurrences mentioned but not quantified).

This form of adjuvant treatment is delivered by spraying liquid nitrogen into the curettaged cavity in order to extend the surgical margin. The associated temperature injury will kill residual tumor cells.

Basic research has been done to investigate the extent of histological changes in frozen bone segments in vivo. Malawer et al showed in experiments with dogs

that liquid nitrogen was capable of inducing trabecular and bone necrosis, extending 7-12 mm around the circumference of a cavity representing a bone cyst.[29] The minimum temperature necessary for a cytotoxic effect is believed to be -50 to -60 C for invasive cancer cells [30] and rapid cooling (more than 100 degrees per minute) increases cell death.[31] In some centers cryosurgery is utilized by pouring liquid nitrogen directly into the bony cavity. A spray delivery was used in this series because it enables increased contact of the coolant with the irregular walls of the cavity and allows better appreciation and control of the extent of the freeze.

Although the benefit of the cryosurgical technique has been recognized for some time, it has not been practiced widely in orthopaedic oncology. This is due to limited experience and concerns regarding a high incidence of complications.[32,33] While complications due to nitrogen embolism have been reported, they were not observed in our patients.[27,34] One patient in our series did suffer a partial radial nerve palsy that completely resolved spontaneously. We agree with Marcove that the complication rate has been significantly lowered with greater experience.[26]

All patients except two in this series had their bony defect grafted with allogenic bone chips. In general, bony healing was rapid and relatively complete.[35] There were no cases of postoperative osteolysis which were not associated with tumor recurrence. We did not recognize any other complications attributed to the use of this graft material. Patients and their families were carefully informed regarding the small risk of potential disease transmission with allogenic bone grafts and all patients receiving allograft, consented to its use. Based on this experience we continue to encourage patients and their families to consider allogenic freeze-dried chips as the graft of choice.

patient	age year	gender	site	size cm	time to recurrence			outcome
					firs	second	third	
JL	8	female	diaphysis humerus	5	23	-	-	A
GB	6	male	prox. metaph. humerus	4.5	4	9	-	OR scheduled
CJ	11	male	diaphysis humerus	5	4	8	-	A
PM	8	male	diaphysis femur	4	11	11	8	A
SB	16	male	prox. metaph. humerus	9	4	-	-	A

Table 6.4: Survey of patients with local recurrence, further treatment and outcome.

We believe that the use of cryosurgery as an adjuvant therapy in the surgical treatment of SBC is of significant value. Using this technique we have experienced a local recurrence rate of 12%, which is lower than the overall mean recurrence rate of published series of 29% for curettage and bone grafting. Local recurrences that did occur were typically recognized (4 out of 5) within twelve months after surgery. These results were achieved in a group of patients who had

a relatively high fracture rate and had failed prior treatment in 38% of the patients. Considering this relatively high risk group of patients we think that our local tumor control represents an improvement over past published techniques.

REFERENCES

1 **Scaglietti O, Marchetti PGM, BartolozziP.** Final results obtained in the treatment of bone cysts with methylprednisolone acetate (Depo-Medrol) and a discussion of results achieved in other bone lesions . Clin Orthop 1982; 165: 33-42.

2 **Scaglietti O, Marchetti PGM, Bartolozzi P.** The effects of methylprednisolone acetate in th e treatment of bone cysts. J Bone Joint Surg 1979; 61: 200-4.

3 **Campanacci M, Capanna R, Picci P.**Unicameral and aneurysmal bone cysts. Clin Orthop 1986; 204: 25-36.

4 **Bovill DF, Skinner HB.**Unicameral bone cysts. A comparison of treatment options. Orthop Rev 1989; 18: 420-7.

5 **Pentimalli G, Tudisco C, Scola E, Farcetti P, Ippolito E.**Unicameral bone cysts--compariso n between surgical and steroid injection treatment. Arch Orthop Trauma Surg 1987; 106: 251-6.

6 **Inoue O, Ibaraki K, Shimabukuro H, Shingaki Y.**Packing with high-porosity hydroxyapatite cube s alone for the treatment of simple bone cysts. Clin Orthop 1993; 293: 287-92.

7 **Oppenheim WL, Galleno H.** Operative treatment versus steroid injection in the management o f unicameral bone cysts. J Pediatr Orthop 1984; 4: 1-7.

8 **Spence KF Jr, Bright RW, Fitzgerald SP, Sell KW.**Solitary unicameral bone cyst: treatment wit h freeze-dried crushed cortical-bone allograft. A review of one hundred and forty-four cases. J Bon e Joint Surg Am 1976; 58: 636-41.

9 **Spence KF, Sell KW and Brown RH.**Solitary bone cyst: treatment with freeze-dried cancellous bone allograft. A study of one hundred seventy-seven cases. J Bone Joint Surg 1969; 51: 87-96.

10 **Neer CS II, Marcove RC, Terz and Carbonara PN.**Treatment of unicameral bone cyst. A follow-u p study of one hundred seventy-five cases. J Bone Joint Surg 1966; 48: 731-745.

11 **Mylle J, Burssens A, Fabry G.** Simple bone cysts. A review of 59 cases with special reference t o their treatment. Arch Orthop Trauma Surg 1992; 111: 297-300.

12 **Morton KS.** Unicameral bone cyst. Can J Surg 1982; 25: 330-2.

13 **Enneking WF.** A system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

14 Technical Manual Tissue Banking, Musculo-skeletal tissue section. American Association Tissue Banking, February 1992.

15 **Gartland JJ and Cole FL.** Modern concept in the treatment of unicameral bone cysts of the proxima l humerus. Orthop Clin North Am 1975; 6: 487-98.

16 **Ahn JI, Park JS.** Pathological fractures secondary to unicameral bone cysts. Int Orthop 1994; 18: 20-2.

17 **Cohen J.** Etiology of simple bone cyst. J Bone Joint Surg Am 1970; 52: 1493-97.

18 **Ekkernkamp A, Muhr G and Lies A.** Die kontinuierliche Dekompression. Ein neuer Weg in de r Behandlung juveniler Knochenzysten. Unfallchirurg 1990; 93: 539-43.

19 **Chigira M, Shimizu T, Arita S, Watanabe H, Heshiki A.**Radiological evidence of healing of a simple bone cyst after hole drilling. Arch Orthop Trauma Surg 1986; 105: 150-3.

20 **Mirra JM, Bernard GW, Bullough PG, Johnston W and Mink G.**Cementum-like bone productio n in solitary bone cyst. (Socalled "cementum" of long bones.) Report of three cases. Electro n microscopic observations supporting a synovial origin to the simple bone cyst. Clin Orthop 1978; 135: 295-307.

21 **Komiya S, Tsuzuki K, Mangham DC, Sugiyama M, Inoue A.** Oxygen scavengers in simple bone cysts. Clin Orthop 1994; 308: 199-206.
22 **Kaelin AJ, MacEwen GD.** Unicameral bone cysts. Natural history and the risk of fracture. Int Orthop 1989; 13: 275-82.
23 **Capanna R, Sudanese A, Baldini N, Campanacci M.** Phenol as an adjuvant in the control of local recurrence of benign neoplasms of bone treated by curettage. Ital J Orthop Traumatol 1985; 11: 381-8.
24 **Schiller CH, Ritschl P, Windhager R, Kropej D, Kotz R.** Frequency of recurrence in phenolized and nonphenolized bone cavities following intralesional excisions of nonmalignant bone tumors. Z Orthop 1989; 127: 398-401.
25 **Rock MG.** Treatment of bone cysts and giant cell tumors. Current Opinion in Orthopaedics 1990; 1: 423-34.
26 **Marcove RC, Weis LD, Vaghaiwalla MR, Pearson R.** Cryosurgery in the treatment of giant cell tumors of bone. A report of 52 consecutive cases. Clin Orthop 1978; 134: 275-89.
27 **Marcove RC.** A 17- Year review of cryosurgery in the treatment of Bone Tumors. Clin Orthop 1982; 163: 231-4.
28 **Malawer MM, Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors. Clin Orthop 1991; 262: 42-57.
29 **Malawer MM, Marks MR, McChesney D, Piasio M, Gunther SF and Schmookler BM.** The effect of cryosurgery and polymethylmethacrylate in dogs with experimental bone defects comparable to tumor defects. Clin Orthop 1988; 226: 299-310.
30 **Gage AA.** Cryosurgery for cancer. Comprehensive Therapy 1984; 10: 61-9.
31 **Kerschbaumer F, Russe W, Weiser G, Bauer R.** Cryolesions of bone. Arch Orthop Traumat Surg 1980; 96: 5-9.
32 **Gage AA and Erickson RB.** Cryotherapy and curettage for bone tumors. J Cryosurgery 1968; 1: 60-66.
33 **Marcove RC, Lyden JP, Huvos AG and Bullough PG.** Giant cell tumors treated by cryosurgery. J Bone Joint Surg 1973; 55: 1633-44.
34 **Schreuder HWB, van Beem HBH, Veth RPH.** Venous gas embolism during cryosurgery for bone tumors. J Surg Oncol 1995; 60: 196-200.
35 **Glancy GL, Brugioni DJ, Eilert RE, Chang FM.** Autograft versus allograft for benign lesions in children. Clin Orthop 1991; 262: 28-33.

CHAPTER 7

ANEURYSMAL BONE CYSTS TREATED BY CURETTAGE, CRYOTHERAPY AND BONE GRAFTING

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ABSTRACT

We treated 26 patients with 27 aneurysmal bone cysts by curettage and cryotherapy and evaluated local tumour control, complications and functional outcome. The mean follow-up time was 47 months (19-154). There was local recurrence in one patient. Two patients developed deep wound infections and one had a postoperative fracture.
We compared our results with previous reports in which several different methods of treatment had been used and concluded that curettage with adjuvant cryotherapy had similar results to those of marginal resection, and that no major bony reconstruction was required.
We recommend the use of cryotherapy as an adjuvant to the surgical treatment of aneurysmal bone cysts. It provides local tumour control. Combination with bone grafting achieved consolidation of the lesion in all our patients.

INTRODUCTION

Aneurysmal bone cyst is a rare benign tumour-like lesion of bone of unknown origin. There is controversy as to whether it is a distinctive radiological and pathological entity or a pathophysiological change superimposed on a pre-existing lesion.[1] Lack of understanding about its origin and growth makes treatment empirical. The most common treatment has been curettage with bone grafting which has a substantial rate of recurrence.[2-6] Lower recurrence rates can be achieved by marginal or wide resection, but are accompanied by loss of bone

and the need for reconstruction.[2,7,8] Intralesional resection or curettage with effective adjuvant therapy to extend the surgical margin has been advocated.[5,9] Since 1969 we have used cryotherapy as an adjuvant therapy after intralesional resection and we now evalute our results.

PATIENTS AND METHODS

We performed a retrospective study of all patients treated for aneurysmal bone cyst between 1969 and 1995. This included review of all patient records, radiographs and pathology reports. The diagnosis had been made on both radiological and histological examination. Only patients with the diagnosis aneurysmal bone cyst and no other abnormal histological findings were included. There were 12 females and 14 males (27 aneurysmal bone cysts). The mean age at which cryotherapy was first performed was 21.7 years (4.2 - 49.6) and the distribution is shown in Table 7.1. The bones involved are shown in Table 7.2.
All had been treated by curettage and cryotherapy. Age, gender, history, anatomical location, tissue pathology, complications, function after surgery and length of follow-up had been recorded. Staging was accomplished using the radiological criteria for benign lesions of bone defined by Enneking.[10]

Author	N	male	femal	age (years)					
				0-10	11-20	21-30	31-40	41-50	> 51
Campanacci et al[9]	198	83	115	63	94	20	12	8	1
Koskinen et al[11]	20	13	7	3	9	2	3	2	1
Martinez and Sissons[12]	87	45	42	25	39	14	3	2	4
Morton[13]	26	14	12	12	6	4	2	2	-
Nobler et al[14]	33	13	20	3	-	17	7	6	-
Ruiter et al[6]	105	46	59	39	50	13	2	-	1
Szendröi et al[8]	52	31	21	15	25	6	2	1	3
Vergel De Dios et al[15]	238	109	129	57	132	30	6	6	7
Schreuder et al	26	14 (54%)	12 (46%)	5 (19%)	10 (38%)	5 (19%)	2 (8%)	4 (15%)	-
Total	785	368	417	222	365	111	39	31	17
Percentages of totals:		46.9	53.1	28.3	46.4	14.1	5.0	3.9	2.2

Table 7.1: Details of studies on aneurysmal bone cysts.

Operative treatment consisted of intralesional resection (curettage) after bony fenestration, followed by cryotherapy. Initially, this had been used by one (2 cases), two (4 cases) or three (2 cases) freeze/thaw cycles, pouring liquid nitrogen into the bony cavity. In the subsequent 19 cases, we used three cycles of freezing and spontaneous thawing with a machine which produced a liquid nitrogen spray. The progress of freezing was usually monitored by thermocouples. A temperature of less than -50°C inside the cavity was considered to be lethal for remaining tumour cells. A thermocouple outside the cavity, preferably close to the neurovascular bundle, was used to prevent freezing of these structures. In many cases the cavity was filled with an autograft (4) or allograft (14) of bone. Spondylodesis was performed once. Preoperative antibiotic prophylaxis was used in all patients (Kefzol; Eli Lilly Nederland BV, Nieuwegein, The Netherlands).
Occlusive tourniquets were not used. Patients were not allowed to bear weight on the affected limb until there were signs of radiological consolidation.
The mean clinical follow-up was 47.4 months (19-154). Two patients had a follow-up of less than 24 months (19 and 22). Conventional plain radiography was used in the follow-up period. Functional assessment was performed at the most recent follow-up visit and consisted of operation-related complaints and physical examination.

Author	**tibia**	**femur**	**vertebra**	**pelvis**	**humerus**	**fibula**	**foot**	**hand**	**ulna+radius**	**other**	**N**
Biesecker et[17]	8	8	4	8	14	3	6	2	6	7	66
Campanacci et al[2]	48	35	20	28	15	14	8	8	9	13	198
Cole[7]	5	2	-	6	4	2	-	-	4	2	25
Farcetti et al[18]	1	5	2	-	-	1	4	-	2	5	20
Koskinen et al[11]	3	3	1	2	6	2	1	-	1	1	20
Martinez et al[12]	19	12	13	8	6	4	5	5	10	5	87
Morton[13]	6	5	5	1	1	3	3	-	1	1	26
Nobler et al[14]	4	6	2	7	3	1	4	-	3	3	33
Ruiter et al[6]	15	13	14	8	7	11	7	10	5	15	105
Szendröi[8]	8	6	4	7	8	5	4	2	6	2-	52
Vergel De Dios et al[15]	34	40	34	26	14	18	13	15	15	29	238
Schreuder et al	6 22%	8 30%	2 7%	3 11%	4 15%	2 7%	2 7%	-	-	-	27
Total	157	143	101	104	82	66	57	42	62	73	897
Percentage:	**17.5**	**15.9**	**11.2**	**11.6**	**9.1**	**7.3**	**6.3**	**4.7**	**6.9**	**9.2**	

Table 7.2: Anatomical distribution of aneurysmal bone cysts.

RESULTS

We classified 11 aneurysmal bone cysts as aggressive and 16 as active. The presenting symptom was a pathological fracture in seven patients, pain or discomfort due to swelling in 17 patients and neurological symptoms in two (both of whom had vertebral lesions). There was only one local recurrence, a rate of 3.7%. This cyst had been treated with only one cycle of cryotherapy using the pouring technique.
Complications included two cases of deep wound infections (7.4%). Both were successfully treated by debridement and the implantation and subsequent removal of gentamicin-PMMA beads. After a fall due to breakage of a crutch handle one patient had a femoral fracture through the treated lesion; this was treated successfully by osteosynthesis. One patient with a sacral lesion had a temporary increase in neurological symptoms which resolved within three months. All bone grafts showed progressive consolidation and incorporation. At the most recent follow-up, 24 patients had normal function of the treated limb without discomfort. One had some loss of movement at the hip and one at the ankle. All patients resumed normal daily activities.

DISCUSSION

Aneurysmal bone cysts is common in adolescents and almost half of the patients are between 10 and 21 years of age.[2,6,8,11-15] There is a slight predilection for females (Table 7.1), and great varibility in the clinical course. In most cases there is pain and swelling and sometimes a pathologic fracture. When located in the vertebral column neurological symptoms, as well as pain, are likely to be present. Aneurysmal bone cysts can occur in any bone, bur are more common in the metaphysis of the long bones, especially around the knee, and in the vertebral column (Table 7.2). The demographic characteristics of our series do not differ significantly from the typical picture reported in the literature.
Aneurysmal bone cysts both erode and cause "expansion" of underlying cancellous and cortical bone.[2] Around the lesion there is always a shell formed by periosteal new bone and, although this may be only millimeters thick, it prevents direct extension into the soft tissues.[16]
The concept of aneurysmal bone cyst as a secondary phenomenon occurring in a preexisting lesion is based on the fact that in approximately one-third of the cases a pre-existing lesion can be identified, the most common of which is giant cell tumour.[1] Others are osteoblastoma, angioma and chondroblastoma.[1,12,17] Less common assosiations include fibrous dysplasia, non-ossifying fibroma, chondromyxoid fibroma, solitary bone cyst, fibrous histiocytoma, eosinophilic granuloma, radiation osteitis and trauma. Malignant lesions, such as osteosarcoma (especially telangiectatic), fibrosarcoma and metastatic carcinoma may have similar radiological and histological features to aneurysmal bone cyst,[6] so accurate diagnosis is essential before advising treatment.

Author	irradiation		curettage + irradiation		curettage + or - bonegraft		curettage + cryosurgery		marginal resection		wide resection		mean follow-up (months)	time to first recurrence (months)
	N	R	N	R	N	R	N	R	N	R	N	R		
Campanacci et al [2]	8	2	15	3	91	19	-	-	47	0	-	-	84	2-72
Cole[7]	-	-	1	0	18	7	-	-	4	0	2	0	> 24	75% < 24
Clough and Price [3]	1	0	2	0	15	8	-	-	3	0	-	-	79	5-48
Farcetti et al [18]	-	-	3	0	11	2	-	-	-	-	6	0	116	3-4
Freiberg et al [4]	-	-	-	-	7	5	-	-	-	-	-	-	> 24	< 14
Koskinen et al [11]	-	-	1	0	14	2	-	-	-	-	5	0	54	-
Kreicbergs et al [19]	-	-	-	-	21	8	-	-	-	-	-	-	> 24	-
van Loon et al [20]	1	0	-	-	8	3	-	-	-	-	1	0	102	7-15
Marcove et al [5]	11	1	-	-	44	26	51	9	-	-	-	-	85	3-102
Nobler et al [14]	6	1	1	0	18	6	-	-	4	2	4	0	-	-
Ruiter et al [6]	2	0	-	-	82	28	-	-	17	4	4	0	80% > 24	-
Slowick et al [21]	4	0	-	-	5	1	-	-	-	-	4	0	83	10
Szendröi et al [8]	-	-	-	-	26	7	-	-	6	0	16	0	> 24	14
Vergel De Dios et al [15]	1	0	12	2	124	27	-	-	-	-	17	0	> 24	90% <24
Schreuder et al	-	-	-	-	-	-	27	1	-	-	-	-	47	36
Total:	34	4	36	5	484	149	78	10	81	6	59	0		
Recurrence rates (%):	**11.8%**		**13.8%**		**30.8%**		**12.8%**		**7.4%**		**0%**			

Table 7.3: Different types of treatment (N) and recurrence tates (R) of aneurysmal bone cysts.

We agree with the view that aneurysmal bone cyst is an entity on its own[2] having unique clinical, radiological and diagnostic behavior. The diagnosis should be made only after the exclusion of an underlying lesion which can produce similar features. Such other conditions should be labelled after their principal element with the added description "cystic or hemorrhagic changes".[2] Our study included only primary aneurysmal bone cysts with no other histological findings.

Because of this lack of understanding about the origin and growth of aneurysmal bone cysts a variety of treatments has been described. They include irradiation alone, or a primary surgical approach with or without some kind of adjuvant treatment. Theoretically, adjuvant therapy may consist of systemic chemotherapy, radiotherapy and physical adjuvants like phenol, hypertonic saline merthiolate, polymethylmethacrylate (PMMA) cement applied locally, and cryotherapy.

Chemotherapy and irradiation therapy have an effect on mitotically-active cells. Their influence on a benign lesion such as aneurysmal bone cyst is limited and we believe that they are inappropriate because of the side-effects. Although radiation therapy has been used, especially in sites of difficult surgical access, with good results (Table 7.3), we do not advise it because of the risk of secondary sarcoma in the irradiated field.

Phenol is a non-selective cytotoxic agent and when applied directly to the surface of curetted tumours, it kills remaining residual tumour and normal cells. Used as an adjuvant after curettage of aneurysmal bone cysts, the reported recurrence rate is 12.5% to 20%.[22,23] Recurrence is probably due to its superficial action and the impossibility of penetrating the periphery beyond surgical margin.

The rationale of the use of PMMA cement as adjuvant treatment is based on its heating effect. Experiments have shown that a thermal lesion of at least 50°C is necessary for a cytotoxic effect. The maximum peripheral extent of a thermal lesion varies from 2.5 mm in cancellous to only 0.5 mm in cortical bone.[24] For local control of giant-cell tumour good results with recurrence rates of 5% to 15% have been reported,[24,25] but no results are available for the use of PMMA cement as adjuvant treatment of aneurysmal bone cysts.

The most commonly used treatments and their recurrence rates are summarized in Table 7.3. The recurrence rate for irradiation with or without curettage are similar, respectively 11.8% and 13.8%. Curettage with or without bone grafting is accompanied by a high recurrence rate of 30.8%. Cryotherapy as an adjuvant after curettage has a recurrence rate of 12.8%. Marginal and wide resection are associated with low recurrence rates, 7.4% and 0% respectively. In review of 65 cases of aneurysmal bone cysts in the facial region,[26] curettage was associated with a recurrence rate of 33%, about the same as for non-facial lesions.

Cryotherapy using liquid nitrogen has been used for the treatment of benign stage-2 (active), stage-3 (aggressive) and low-grade malignant stage IA skeletal tumours.[27-30] It is often advocated to avoid extensive surgical destruction of tissue.[26-30] Intralesional resection is performed by curettage. Adjuvant treatment is currently given by spraying liquid nitrogen into the bony cavity. This method

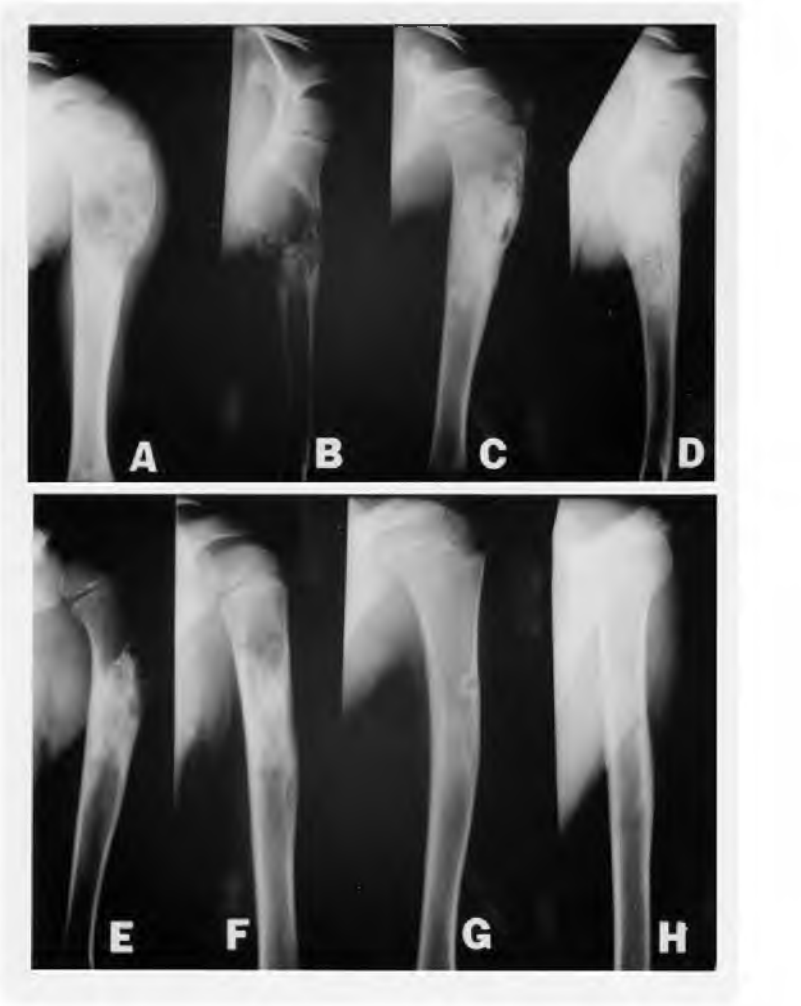

Figure 7.1: Initial antero-posterior (A) and lateral (B) radiographs of an aneurysmal bone cyst in the proximal metaphysis of the left humerus of a four-year-old-boy three months after curettage, cryotherapy and bone allograft (C and D). One year (E and F) and four years (G and H) the bone has completely remodelled and the appearance of the intramedullary space is almost normal.

must be considered marginal by oncologic principles.[10] The advantage, compared with local resection, is that the supportive function of bone is preserved and reconstructive surgery can be limited. In studies on the extent of the effect of freezing on bone segments in vivo, Gage[31] found that the temperature gradient was steep and that at approximately 2 cm from the freezing source no freezing of bone occurred, even after 15 minutes of freezing. All the frozen bone was devitalized within one week. Osteogenesis originating from normal bone and periosteum adjacent to the frozen segment, however, was seen within several days. Revitalization by simultaneous resorption and reossification took several months.[31,32] The minimum temperature necessary for a cytotoxic effect on invasive cancer cells is believed to be -50°C to -60°C.[33] Rapid cooling (more than 100°/min) and slow thawing (1°C to 10°C/min) allows the highest cell death rates.[32,34] The freeze and thaw cycles must be repeated several times because living tissue is able to resist thermal injury and it is technically difficult to achieve optimal conditions for cell death in all areas of the lesions. To compensate, repetition of freeze thaw cycles is a practical solution and is safe especially at the periphery of the lesion.[34-36] In the early days of cryotherapy liquid nitrogen was poured directly into a curetted tumour cavity.[28] We prefer spraying liquid nitrogen, in every direction needed, because it increases the contact area with the irregular walls of the cavity, and the freezing process is more easily controlled.

Although the cryotherapeutic technique and its potential benefits have been known for a long time, it is infrequently adopted in orthopaedic practice. This is probably due to the high incidence of complications, especially postoperative fractures and wound infections, that have been reported.[26,28] Among our patients there was one postoperative fracture due to trauma. There were two deep infections which needed additional surgery. We do not use tourniquets, in order to keep nerves and skin vascularized and thereby protect them from freezing injury. Nerve injuries appear to recover completely. Gas embolism is possible, and there has been one reported mortality.[29,37] The complication rate becomes less as experience with cryotherapy increases.[27]

We found that cryotherapy as an adjuvant to curettage of aneurysmal bone cysts is associated with a local recurrence rate of 4%. The only recurrence we had was probably due to technique as only one cycle of cryotherapy had been used. Marcove et al[5] reported a recurrence rate of 18% which after additional treatments with the same technique decreased to 4%. Marginal and wide resection of aneurysmal bone cysts lead to comparable local control, but more extensive reconstructive surgery is then needed, with associated morbidity. In general, we recommend the use of cryotherapy as an adjuvant to curettage for the treatment of aneurysmal bone cysts (Figure 7.1). The use of a bone graft allowed for consolidation in all cases. In expendable bones (e.g. proximal fibula, ribs) marginal resection appears to be sufficient.[2] Superselective embolization with or without irradiation may be considered for aneurysmal bone cysts located in anatomic positions which are very difficult to treat surgically, like vertebral and sacral lesions.[2,8,14]

REFERENCES

1 **Kransdorf MJ, Sweet DE.** Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging. Am J Roentgenol 1995; 164: 573-80.

2 **Campanacci M, Capanna R, Picci P.** Unicameral and aneurysmal bone cysts. Clin Orthop 1986; 204: 25-36.

3 **Clough JR, Price CHG.** Aneurysmal bone cysts: Pathogenesis and long term results of treatment. Clin Orthop 1973; 97: 52-63.

4 **Freiberg AA, Loder RT, Heidelberger KP, Hensinger RN.** Aneurysmal bone cysts in young children. J Pediatr Orthop 1994; 14: 86-91.

5 **Marcove RC, Sheth DS, Takemoto S, Healey JH.** The treatment of aneurysmal bone cyst. Clin Orthop 1995; 311: 157-63.

6 **Ruiter DJ, van Rijssel ThG, van der Velde EA.** Aneurysmal bone cysts. A clinicopathological study of 105 cases. Cancer 1977; 39: 2231-9.

7 **Cole WG.** Treatment of aneurysmal bone cysts in childhood. J Pediatr Orthop 1986; 6: 326-9.

8 **Szendröi M, Cser I, Konya A, Renyi-Vamos A.** Aneurysmal bone cyst. A review of 52 primary and 16 secondary cases. Arch Orthop Trauma Surg 1992; 111: 318-22.

9 **Oeseburg HB, Rogge CWL, Schraffordt Koops H, Oldhoff J.** Cryosurgical treatment of aneurysmal bone cysts. J Surg Oncol 1978; 10: 9-20.

10 **Enneking WF.** A system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

11 **Koskinen EV, Visuri TI, Holmstrom T, Roukkula MA.** Aneurysmal bone cyst: evaluation of resection and of curettage in 20 cases. Clin Orthop 1976; 118: 136-46.

12 **Martinez V, Sissons HA.** Aneurysmal bone cysts. A review of 123 cases including primary lesions and those secondary to other bone pathology. Cancer 1988; 61: 2291-2304.

13 **Morton KS.** Aneurysmal bone cyst: a review of 26 cases. Can J Surg 1986; 29: 110-5.

14 **Nobler MP, Higinbotham NL, Phillips RF.** The cure of aneurysmal bone cyst. Irradiation superior to surgery in an analysis of 33 cases. Radiology 1968; 90: 1185-92.

15 **Vergel De Dios AM, Bond JR, Shives TC, McLeod RA, Unni KK.** Aneurysmal bone cyst. A clinicopathologic study of 238 cases. Cancer 1992; 69: 2921-31.

16 **Enneking WF.** Aneurysmal bone cyst. In: Musculoskeletal Tumor Surgery. New York: Churchill Livingstone, 1983: 1513-29.

17 **Biesecker JL, Marcove RC, Huvos AG, Miké V.** Aneurysmal bone cysts. A clinicopathologic study of 66 cases. Cancer 1970; 26: 615-25.

18 **Farsetti P, Tudisco C, Rosa M, Pentimalli G, Ippolito E.** Aneurysmal bone cyst. Long-term follow-up of 20 cases. Arch Orthop Trauma Surg 1990; 109: 221-3.

19 **Kreicbergs A, Lonnqvist PA, Nilsson B.** Curettage of benign lesions of bone. Factors related to recurrence. Int Orthop 1985; 8: 287-94.

20 **van Loon CJM, Veth RPH, Pruszczynski M, van Horn JR, Lemmens JAM.** Aneurysmal bone cyst. Long-term results and functional evaluation of 16 primary cases in 13 patients. Acta Orthop Belgica 1995; 61: 199-204.

21 **Slowick FA Jr, CampbellCJ, Kettelkamp DB.** Aneurysmal bone cyst. An analysis of thirteen cases. J Bone Joint Surg Am 1968; 50: 1142-51.

22 **Schiller CH, Ritschl P, Windhager R, Kropej D, Kotz R.** Frequency of recurrence in phenolized and nonphenolized bone cavities following intralesional excisions of nonmalignant bone tumors. Z Orthop 1989; 127: 398-401.

23 **Capanna R, Sudanese A, Baldini N, Campanacci M.** Phenol as an adjuvant in the control of local recurrence of benign neoplasms of bone treated by curettage. Ital J Orthop Traumatol 1985; 11: 381-8.

24 **Rock MG.** Treatment of bone cysts and giant cell tumors. Current Opinion in Orthopaedics 1990; 1: 423-34.

25 **Malawer MM, Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors, Analysis of 25 patients below the age of 21. Clin Orthop 1991; 262: 42-57.

26 **Trent C, Byl FM.** Aneurysmal bone cyst of the mandible. Ann Otol Rhinol Laryngol 1993; 102: 917-24.

27 **Marcove RC, Stovell PB, Huvos AG, Bullough PG.** The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. A preliminary report. Clin Orthop 1977; 122: 147-56.

28 **Marcove RC, Weis LD, Vaghaiwalla MR, Pearson R.** Cryosurgery in the treatment of giant cel l tumors of bone. A report of 52 consecutive cases. Clin Orthop 1978; 134: 275-89.
29 **Marcove RC.** A 17-Year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1982; 163: 231-4.
30 **Jacobs PA, Clemency Jr RE.** The closed cryosurgical treatment of giant cell tumor. Clin Orthop 1985; 192: 149-58.
31 **Gage AA.** Cryosurgery for cancer. Comprehensive Therapy 1984; 10: 61-9.
32 **Kerschbaumer F, Russe W, Weiser G, Bauer R.** Cryolesions of bone. Arch Orthop Traumat Surg 1980; 96: 5-9.
33 **Gage AA.** What temperature is lethal for cells? J Dermatol Surg Oncol 1979; 5: 459-60.
34 **Neel HB, Ketcham AS, Hammond WG.** Requisites for successful cryogenic surgery of cancer. Arch Surg 1971; 102: 45-9.
35 **Gill W, Frazer J, Carter D.** Repeated freeze-thaw cycles in cryosurgery. Nature 1968; 219: 410-3.
36 **Gage A.** Experimental cryogenic injury of the palate: observations pertinent to cryosurgical destruction of tumors. Cryobiology 1978; 15: 415-25.
37 **Schreuder HWB, van Beem HBH, Veth RPH.** Venous gas embolism during cryosurgery for bon e tumors. J Surg Oncol 1995; 60: 196-200.

CHAPTER 8

EOSINOPHILIC GRANULOMA OF BONE: RESULTS OF TREATMENT WITH CURETTAGE, CRYOSURGERY AND BONE GRAFTING

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ABSTRACT

Intralesional instillation of steroids is currently the first choice of treatment for eosinophilic granuloma of bone. However, some lesions fail to respond or are unsuitable for injection therapy due its location, (pending) pathologic fracture and soft tissue intrusion. We treated six patients with these lesion characteristics with curettage, cryosurgery and bone grafting. After a mean follow-up of 23.3 months all lesion were completely healed, although one femoral fracture eight months after the operation occurred.
In selected cases of eosinophilic granuloma of bone a primary surgical treatment seems feasible. The use of cryosurgery as adjuvant treatment extends the surgical margin and is of value in avoiding local recurrence.

INTRODUCTION

Eosinophilic granuloma (EG) of bone is part of a spectrum of diseases known as Langerhans cell granulomatosis all characterized by proliferation of specific histiocytes, designated as Langerhans type, in normal tissue. These histocyte proliferations, called eosinophilic granuloma can occur unifocal, multifocal and be part of systemic illness known as the Hand-Schüller-Christian disease and Letterer-Siwe disease.[1-3]
The etiology is unknown and therefore its treatment is empirical. Eosinophilic granuloma of bone was most commonly treated with chemotherapy, surgery and irradiation.[4,5] Currently, as in our institution, intralesional instillation of steroids is the first choice of treatment with good results.[3,4,6-8] However, some lesions fail to respond to steroid injection therapy or are unsuitable for injection therapy due to their size, location, loss of bony containment and or soft tissue intrusion.

Especially in case of cortical destruction with pending pathological fracture and possibly neurological damage in spinal cases.[9-13] a primary surgical approach can be the treatment of choice. This study describes six of such patients in whom we performed an intralesional resection by curettage followed by cryosurgery. This local adjuvant treatment extends the surgical margin, without the need for segmental resection. Bone reconstruction is consequently limited and is achieved by auto- or homogeneous bone grafting.

PATIENTS AND METHODS

Six patients (4 males and 2 females) were diagnosed with EG of bone, all proven by biopsy prior to definite treatment. One patient was 23 year of age, the other were children with a mean age of 3.8 year (range: 1.0 -6.8). Five suffered a solitary lesion and one patient had multiple bony lesions, but without any systemic disease. The indications for surgical treatment were pending pathological fracture with loss of cortical containment in all four femoral lesions, one with no response to steroid injection, extreme aggressive behavior with cortical destruction and extensive soft tissue intrusion of an ulnar lesion threatening the integrity of the elbow joint. The 23 year old patient had EG in the body of a cervical vertebra (C4). This lesion was treated surgically and stabilized, because spinal locations are associated with collapse of the vertebral body (vertebra plana) with sometimes serious neurological complications.[3,4,9-12,14]
Surgical treatment consisted of curettage of the lesion through cortical fenestration, three cycles of cryosurgery utilizing a spray or closed probe followed by spontaneous thawing. Reconstruction of the defect was done with chip homologous bone grafting in all long bone cases and the cervical case had an autologous strut bone graft.
In four cases local peroperative temperature monitoring using thermocouples mounted in a injection-like needle were used.
Post-operative follow-up was done using routine radiographs and skeletal surveys, magnetic resonance imaging and bone scans at standard intervals.

RESULTS

The mean follow-up of the six patients was 23.3 months (range: 10-47). In all cases the onset of symptoms was pain and functional impairment. Three of the four patients with femoral lesions healed completely, with full range of movement of the treated extremity (Figure 8.1). The fourth patient with a femoral lesion was mobilized with full weightbearing, but suffered a fracture eight months after curettage, cryosurgery and bone grafting, possibly due to a trauma. This fracture was initially treated conservatively, but because of progressive malunion,

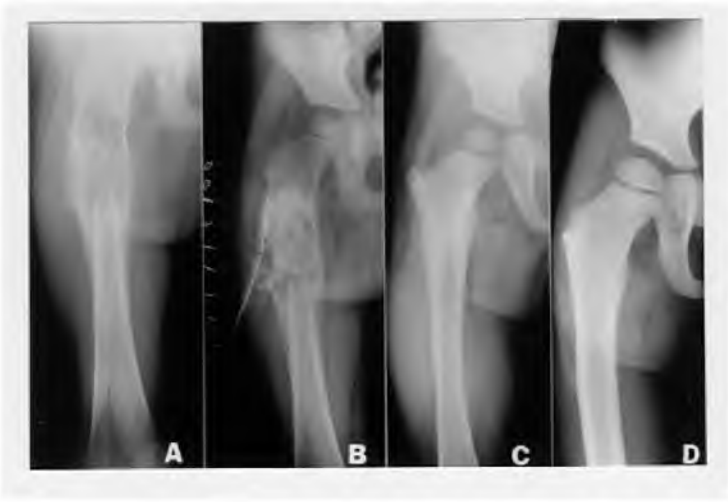

Figure 8.1: Anterior posterior radiographs of right femur of a 6 year old boy. Osteolytic lesion due to EG with pending pathologic fracture (A). After curettage, cryosurgery and homologous bone graft (B). Follow-up at six (C) and 33 (D) months. A complete normalization of the proximal femur has occurred.

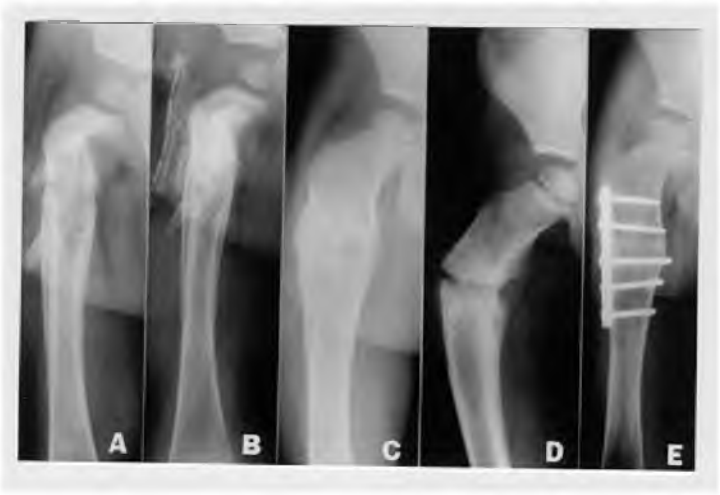

Figure 8.2: Anterior posterior radiographs of right femur of a 2 year old girl.
Osteolytic lesion due to EG, preoperative (A). After curettage, cryosurgery and homologous bone graft (B). Follow-up at 5 months (C). Pathologic fracture 8 months after the operation (D). Consolidation 5 months after internal fixation with plate and screws (E).

osteosynthesis was performed (Figure 8.2), with satisfactory result. Extensive tissue samples taken during this procedure revealed no microscopically evidence for recurrent EG. All four patients with femoral lesions had no radiographic indications for local recurrence at their latest follow-up.
The patient with the ulnar lesion healed completely, with full range of motion of the elbow (Figure 8.3). The patient with the C4 lesion is symptom free with full range of motion 10 months after the treatment, with no evidence for local recurrence. Although the curetted body of C4 was reconstructed with a three cortical iliac crest bone graft a mild local kyphosis of approximately 15 degrees developed (Figure 8.4).
In addition to the mentioned fracture there were no complications.

DISCUSSION

Eosinophilic granuloma represents fewer than one percent of all bone tumor like lesions and its etiology remains unknown.[2,3,15] In contrast to other benign bone lesions its predilection sites are the skull and ribs.[2,4,15-17] However, its occurrence in long bones and spine is frequent enough to pose difficulties in diagnosis, in part of radiologic variability.[2,4,15] Males are predominantly affected and in general the lesions occur in the first decade of life, patients beyond 30 years are exceptional.[2,15,17,18]
Patients with EG of bone frequently present with local pain, tender swelling, functional impairment and occasionally with a (pending) pathological fracture.[3,4,8,15,17]
A major problem in this disorder is the possibility of misdiagnosis.[17] The differential diagnosis includes chronic infection and malignant bone tumors like Ewing sarcoma and osteosarcoma in children and adolescents, in adults other primary bone tumors, myeloma, malignant lymphoma (Hodgkin) and metastatic disease.[2,3,15]
Treatment modalities described for EG are curettage,[2,4,15,16] radiotherapy[15,17] and chemotherapy[5] and combinations of these modalities.[5,15,16,19] Radiotherapy is effective,[20] although second primary neoplasm have been reported.[4,18] Therefore its use should be limited to sites difficult accessible to surgery.
The rational of intralesional injection with corticosteroids is based on the assumption that EG is an (auto)immunologic disorder.[6,15,17] This treatment is effective, safe and convenient with only little reported complications.[3,6,8,15]
Patients with only local or multifocal disease involving only the skeleton have an excellent prognosis,[14] multiple sites of soft tissue involvement is not unfavorable, as long as the liver is spared.[16,21-24]
We treated six patients with EG of bone surgically, because we felt that these lesions, as explained earlier, were unsuitable for corticosteroid injection therapy. The use of cryosurgery as local adjuvant treatment to intralesional curettage extends the surgical margin. By this method the procedure can be considered to be marginal from the point of view of orthopaedic oncologic principles.[25]

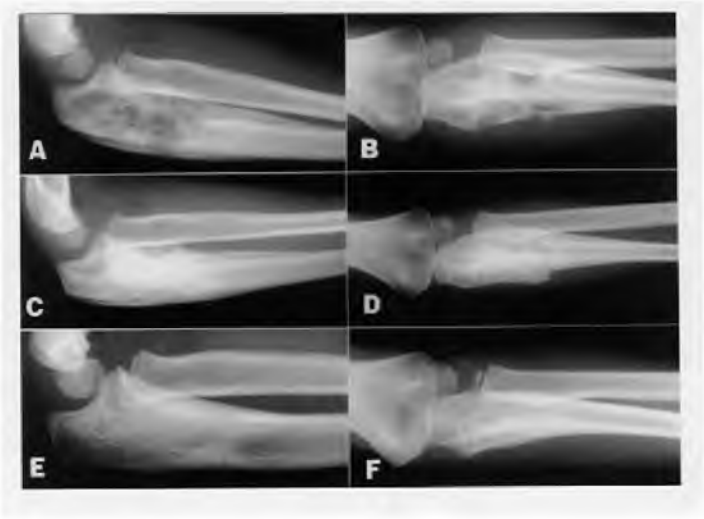

Figure 8.3: Anterior posterior and lateral radiographs of left elbow of a 3.5 year old boy. EG lesio n close to joint (A,B). Follow-up at 7 months after curettage, cryosurgery and homologous bone graft (C,D) and at 15 months (E).

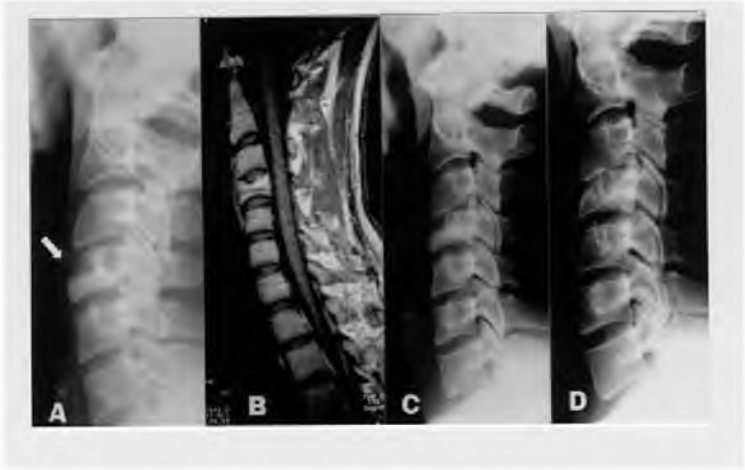

Figure 8.4: Lateral radiograph of cervical spine of 23 year old man. Lytic lesion of body C4 (A). T 1 weighed magnetic resonance image, partial collapse of body (B). Follow-up at 4 months afte r curettage, cryosurgery and autologous strut bone graft (C) and at 10 months (D).

The advantage of this kind of treatment, as compared to local segmental resection, is that as much as possible of the supportive function of bone is preserved and thatreconstructive surgery can be limited. In orthopaedic oncology it is used for the treatment of benign and low-grade malignant stage IA skeletal tumors.[25-33]

Basic research on animals has been done to investigate the histological changes of bone segments in vivo. Histologically all the frozen bone is devitalized within one week after the freeze. On the other hand, osteogenesis originated from normal bone and periosteum adjacent to the previously frozen segment, was seen within several days.[34] The revitalization by simultaneous resorption and re-ossification took several months.[34,35] The minimum temperature necessary for a lethal effect is believed to be minus 50 to 60 Celsius for invasive cancer cells.[36] Rapid cooling (more than 100 degrees per minute) and slow thawing (1-10 degrees per minute) facilitates the highest cell death rates.[35,37] It is necessary to repeat the freeze and thaw cycles several times because living tissue is capable of resisting thermal injury and it is technically difficult to achieve optimal conditions for cell death in all areas of the lesions. To compensate, repetition of freeze thaw cycles is a practical solution and creates safety especially at the periphery of the lesion.[37,38]

In the cervical spine case, with the vicinity of the spinal cord, a closed cryoprobe was used because the extent of the freezing-process is more easily controlled. In general we use a machine producing a liquid nitrogen spray, which increases the contact of the coolant with the irregular walls of the curetted lesion.

The use of cryosurgery as adjuvant therapy to curettage for EG of bone is to our knowledge only reported before by Marcove.[39] He treated 4 patients and encountered, as we did, no local recurrent disease.

We conclude that in selected cases a primary surgical treatment of EG is justified, especially in case of a pending pathologic fracture of weightbearing bones. The additional use of cryosurgery to an intralesional resection of the tumor is of value in order to diminish the risk for local recurrence.

REFERENCES

1 **Schajowicz F.** Histological typing of bone tumours. Berlin Heidelberg: Springer Verlag, 1993.

2 **Makley JT and Carter JR.** Eosinophilic granuloma of bone. Clin Orthop 1986; 204: 37-44.

3 **Capanna R, Springfield DS, Ruggieri P, Biagini R, Picci P, Bacci G, Giunti A, Lorenzi EG Campanacci M.** Direct cortisone injection in eosinophilic granuloma of bone: a preliminary report on 11 patients. J Pediatr Orthop 1985; 5: 339-42.

4 **Greis PE and Hankin FM.** Eosinophilic granuloma. The management of solitary lesions of bone. Clin Orthop 1990; 257: 204-11.

5 **Sartoris DJ and Parker BR.** Histiocytosis X: rate and pattern of resolution of osseous lesions. Radiology 1984; 152: 679-84.

6 **Cohen M, Zornoza J, Cangir A, Murray JA and Wallace S.** Direct injection of methylprednisolone sodium succinate in the treatment of solitary eosinophilic granuloma of bone: a report of 9 cases. Radiology 1980; 136: 289-93.

7 **Nauert C, Zornoza J, Ayala A and Harle TS.** Eosinophilic granuloma of bone: diagnosis and management. Skeletal Radiol 1983; 10: 227-35.

8 **Egeler RM, Thompson RC Jr, Voute PA and Nesbit ME Jr.** Intralesional infiltration of corticosteroids in localized Langerhans' cell histiocytosis. J Pediatr Orthop 1992; 12: 811-4.
9 **Villas C, Martinez-Peric R, Barrios RH and Beguiristain JL.** Eosinophilic granuloma of the spine with and without vertebra plana: long-term follow-up of six cases. J Spinal Disord 1993; 6: 260-8.
10 **Green NE, Robertson WW Jr and Kilroy AW.** Eosinophilic granuloma of the spine with associated neural deficit. J Bone Joint Surg (Am) 1980; 62: 1198-1202.
11 **Maffulli N, Capasso G and Testa V.** Eosinophilic granuloma of C5 causing cervical cord compression. Eur Spine J 1992; 1: 53-4.
12 **Sweasey TA and Dauser RC.** Eosinophilic granuloma of the cervicothoracic junction (case report). J Neurosurg 1989; 71: 942-4.
13 **Martinez-Lage JF, Poza M, Cartagena J, Vicente JP, Biec F and de las Heras M.** Solitary eosinophilic granuloma of the pediatric skull and spine. The role of surgery. Childs Nerv Syst 1991; 7: 448-51.
14 **McCullough CJ.** Eosinophilic granuloma of bone. Acta Orthop Scand 1980; 51: 389-98.
15 **Shabb N, Fanning CV, Carrasco CH, Guo SQ, Katz RL, Ayala AG, Raymond AK and Cangir A.** Diagnosis of eosinophilic granuloma of bone by fine-needle aspiration with concurrent institution of therapy: a cytologic, histologic, clinical, and radiologic study of 27 cases. Diagn Cytopathol 1993; 9: 3-12.
16 **Matus Ridley M, Raney RB Jr, Thawerani H and Meadows AT.** Histiocytosis X in children: patterns of disease and results of treatment. Med Pediatr Oncol 1983; 11: 99-105.
17 **Rodrigues RJ and Lewis HH.** Eosinophilic granuloma of bone. Review of literature and case presentation. Clin Orthop 1971; 77: 183-92.
18 **Komp DM.** Long-term sequelae of histiocytosis X. Am J Pediatr Hematol Oncol 1981; 3: 165-8.
19 **Tsunematsu Y, Koide R, Watanabe S, Takahashi H, Morikawa Y and Shimizu K.** A clinicopathological study of histiocytosis X. Jpn J Clin Oncol 1984; 14: 633-46.
20 **Richter MP and D'Angio GJ.** The role of radiation therapy in the management of children with histiocytosis X. Am J Pediatr Hematol Oncol 1981; 3: 157-60.
21 **Greenberger JS, Crocker AC, Vawter G, Jaffe N and Cassady JR.** Results of treatment of 127 patients with systemic histiocytosis (Letterer-Siwe syndrome, Schüller-Christian syndrome and multifocal eosinophilic granuloma). Medicine 1981; 60: 311-38.
22 **Slater J and Swarm O.** Eosinophilic granuloma of bone. Med Pediatr Oncol 1980; 8: 151-64.
23 **Bunch W.** Orthopaedic and rehabilitation aspects of eosinophilic granuloma. Am J Pediatr Hematol Oncol 1981; 3: 151-6.
24 **Lieberman PH, Jones CR, Dargeon HWK and Begg.** A reappraisal of eosinophilic granuloma of bone, Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome. Medicine 1969; 48: 375-400.
25 **Enneking WF.** A staging system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.
26 **Jacobs PA and Clemency Jr RE.** The closed cryosurgical treatment of giant cell tumor. Clin Orthop 1985; 192: 149-58.
27 **Malawer MM and Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors. Analysis of 25 patients below the age of 21. Clin Orthop 1991; 262: 42-57.
28 **Marcove RC, Weis LD, Vaghaiwalla MR and Pearson R.** Cryosurgery in the treatment of giant cell tumors of bone. A report of 52 consecutive cases. Clin Orthop 1978; 134: 275-89.
29 **Marcove RC, Sheth DS, Takemoto S, Healey JH.** The treatment of aneurysmal bone cyst. Clin Orthop 1995; 311: 157-63.
30 **Marcove RC, Stovell PB, Huvos AG and Bullough PG.** The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. A preliminary report. Clin Orthop 1977; 122: 147-56.
31 **Schreuder HWB, van Beem HBH and Veth RPH.** Venous gas embolism during cryosurgery for bone tumors. J Surg Oncol 1995; 60: 196-200.
32 **Schreuder HWB, Veth RPH, Pruszczynski M, Lemmens JAM, Schraffordt Koops H and Molenaar WM.** Aneurysmal bone cysts: results of curettage, cryosurgery and bone grafting. J Bone J Surg (Br) 1997; 79: 20-5.

33 **Schreuder HWB, Conrad EU, Bruckner JD, Howlett ATG, Sorensen LS.** The treatment of simpl e bone cysts in children with curettage and cryosurgery. Accepted J Pediatr Orthop.
34 **Gage AA.** Cryosurgery for cancer. Compr Ther 1984; 10: 61-9.
35 **Kerschbaumer F, Russe W, Weiser G, Bauer R.** Cryolesions of bone. Arch Orthop Traumat Surg 1980; 96: 5-9.
36 **Gage AA.** What temperature is lethal for cells? J Dermatol Surg Oncol 1979; 5: 459-60.
37 **Neel HB, Ketcham AS, Hammond WG.** Requisites for successful cryogenic surgery of cancer. Arch Surg 1971; 102: 45-9.
38 **Gill W, Frazer J, Carter D.** Repeated freeze-thaw cycles in cryosurgery. Nature 1968; 219: 410-3.
39 **Marcove RC.** A 17-Year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1982; 163: 231-4.

CHAPTER 9

FEMORAL CHONDROSARCOMA AND TWO ENCHONDROMAS AS SECOND PRIMARY TUMORS IN A BILATERAL RETINOBLASTOMA SURVIVOR

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ABSTRACT:

We describe a bilateral retinoblastoma survivor known for a germline mutation of the retinoblastoma susceptibility gene, who developed after 25 years a chondrosarcoma grade 1 and two aggressive enchondromas in the same femur. In lieu of segmental en block resection which would necessitates a technical demanding reconstruction, the patient was treated with intralesional resection, cryosurgery and bone grafting of all three lesions. After a follow-up of 30 months complete consolidation was observed with no evidence for recurrence.
Since bilateral retinoblastoma survivors have a 15 to 20% risk of developing a second, non-ocular, primary neoplasm in either an irradiated or *non*irradiated field, the resected material was analyzed for DNA mutations by loss of heterozygosity analysis, single strand conformation polymorphism analysis, two-dimensional DNA electrophoresis and sequencing. As expected, the germline of the RB1 gene was also found in the tumor, but no other mutations. To our knowledge this is the first bilateral retinoblastoma survivor ever reported who developed a chondrosarcoma grade 1 and two enchondromas in the same nonirridiated femur.

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INTRODUCTION

In 100 years retinoblastoma has changed from an almost fatal disease to one in which 95% percent of patients can be cured.[1] In 25 to 30% the disease is bilateral and patients always carry a predisposing mutation in the retinoblastoma (RB1) susceptibility gene.[2] Patients with bilateral retinoblastoma have a 15 to 20% risk of developing a second, non-ocular, primary neoplasm in either an irradiated or *non*irradiated field.[2-4] For a long time it has been supposed that these secondary tumors were caused by radiotherapy, but it is now known that they may appear outside the irradiated region and, more important, independent of irradiation. The most common tumor developing in a *non*irradiated field is osteogenic sarcoma.[5] A variety of other second primary tumors like Ewing Sarcoma,[6,7] melanoma,[8] pinealoma,[2] rhabdomyosarcoma,[9] leiomyosarcoma, fibrosarcoma, liposarcoma,[10] lymphoma[11] and epithelioid tumors[12] have been reported. We present a bilateral retinoblastoma survivor in whom after 25 years a chondrosarcoma and two enchondromas in the same femur were diagnosed.

CASE REPORT

A 26 year old female was referred because of patello-femoral pain of the left knee during exercise. General and specific physical examination revealed no serious abnormalities. Conventional radiographs of the knee were normal. The patient was known for bilateral retinoblastoma for which at the age of one year an excision of the right eye and irradiation therapy for the left eye was performed. She is the only known member of a family with a germline mutation of the RB1 gene, being a deletion of cytosine in codon 796 in exon 23, leading to a premature stopcodon and thus to a truncated Rb protein. The remainder of her medical history is noncontributory.

Because of the high incidence of a second primary neoplasm in patients who survived bilateral retinoblastoma, a skeletal scintigraphy with technetium 99m was performed. At the site of the left knee no increased uptake of technetium was observed. Accidently three "hot spots" in the right femur were detected. One lesion was located in the distal part of the diaphysis, one in the distal metaphysis and one in the intertrochanteric area of the proximal metaphysis of the right femur. Inspection of specific X-rays revealed a mixed lytic and calcifying lesion of 2 by 3 centimeter in the distal part of the diaphysis of the right femur. MRI images of the mentioned sites showed evidence for tumors of chondroid origin (Figures 9.1A,B). A biopsy of the lesion in the distal part of the diaphysis was consistent with chondrosarcoma grade 1. The patient was treated with intra-capsular resection, cryosurgery and reconstruction with homologous bonechips of all three lesions. Although ill advised from an oncological point of view, because of potential contamination of the entire femur with tumor cells, it was re-enforced with an intramedullary nail (Figure 9.1C). The loadbearing capacity was impaired due to multiple resections and cryosurgery.

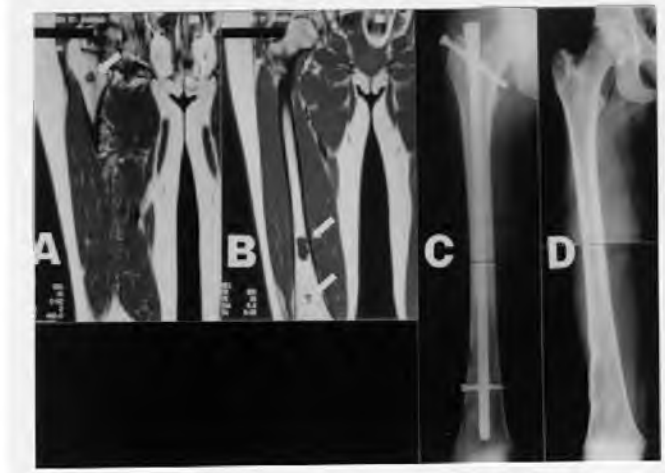

Figure 9.1: MRI - T1 weighted, coronal view. The extent of the intramedullary lesions is accurately depicted. One lesion is located in the distal part of the diaphysis, one in the distal metaphysis (A), and one intertrochanteric in the proximal metaphysis (B). After intralesional resection, cryosurgery and reconstruction with homogeneous bonechips of all three lesions an intramedullary nail is introduced. The proximal locking screw was placed just proximal of the intertrochanteric lesion (C). After removing of the nail, complete normalization of intramedullary space, no evidence for recurrences (D).

At the latest follow-up (30 months), normalization of the intramedullary space was observed with no evidence for recurrence (Figure 9.1D). Histological analysis confirmed chondrosarcoma grade 1 in the previous biopsied lesion and enchondroma in proximal and distal metaphysis.

DNA isolated from the chondrosarcoma was analyzed for mutations. A comparison with leucocyte DNA using the polymorphic intragenic microsatellite markers RB1-2 and RB1-20[13] showed that there was no loss of heterozygosity in the tumor. By single strand conformation polymorphism (SSCP) analysis[14] all but exons 1 and 14 of the RB1 gene have been scanned for mutations, as well as the promoter region and the 3' untranslated part of the gene using newly developed PCR-primers except for the promoter region and exon 2 for which primers were synthesized.[15] An aberrant pattern was only found for exon 23. Sequencing of that exon revealed as expected in one allele the deletion of a cytosine residue in codon 796 of the RB1 gene. All further exons except 1 and 14 have been completely sequenced using a cycle sequencing kit (Amersham) with M13-tailed primers. Two-dimensional DNA electrophoresis of all exons co-amplified by multiplex PCR after pre-amplification by long-distance PCR[16] did not give any indication of further nucleotide variation.

DISCUSSION

Diagnosing a chondrosarcoma grade 1 and two enchondromas in the same bone, we were faced with a difficult problem from a therapeutic point of view. We staged the chondrosarcoma as IA (= low-grade malignant, confined to one anatomical compartment) and both the enchondromas as stage 3 (= aggressive benign).[17] As recommended treatment one might perform a local, preferably wide en bloc resection through normal tissue beyond the reactive zone of the tumor.[17] In our case, with three lesions spread in the femur multifocal resections of the femur and a technical difficult reconstruction with either endoprosthetic or massive allograft would have been necessary. In view of the potential morbidity of this procedure, the low-grade malignant features of this chondrosarcoma and aggressive but benign condition of the other lesions we chose for intracapsular resection of the three lesions, combined with cryosurgery as adjuvant therapy to extend the surgical margins. The value and effectiveness of cryosurgery as adjuvant therapy in orthopaedic oncology has been shown before.[18-21] After an extended review of the literature from 1966 till 1996 using MEDLINE EXPRESS we were unable to find a report of chondrosarcoma in a clearly *non*irradiated area in a patient treated for bilateral retinoblastoma. Chondrosarcoma has been reported in- or very close to the irradiated field in retinoblastoma survivors.[22-24] These chondrosarcomas are considered to be induced by the radiation therapy itself.

Our patient developed 25 years after excision of the right eye and irradiation of the left eye a second primary tumor. From the large series study of the Registry of Ophthalmic Pathology in AFIP it is not only known that the latency period for second nonocular primary tumors varies from 1,4 till 44,3 years (mean 13,4), but also that this period strongly depends on the length of follow-up.[24] In some studies it has been found that after 20 years there is a sharp increase in the incidence of second primary tumors in the nonirradiated field in retinoblastoma survivors.[2,4,10] The role of the RB1 gene in its relation with the high incidence of second primary tumors in retinoblastoma survivors is unclear. Furthermore, a RB1 mutation is found in 20 to 33% of the primary sarcomas in patients not known for retinoblastoma,[25,26] including chondrosarcoma.[27]

Using a combinations of methods that with the possible exception of the GC-rich exons 1 and 14 would certainly have detected a RB1 mutation when present, we could not find a second mutation besides the already identified germline mutation. Exons 1 and 14 were included in the all exon scanning for mutations by two-dimensional DNA electrophoresis, a method which to date never failed in detecting a whole series of known mutations in the CFTR gene,[28] the RB1 gene[16] and the MSH2 and MLH1 genes.[29] Although a definite and complete exclusion of RB1 involvement can never be ensured, the joint development of one chondrosarcoma and the two enchondromas in our patient will most likely be a consequence of dysregulation of one or more as yet unknown genes.

LITERATURE:

1 **Mc Lean IW, Burnier MN, Zimmerman LE, Jakobiec FA.** Tumors of the eye and ocular adnexa, In Atlas of Tumor Pathology, Armed Forces Institute of Pathology, 1994, Third Series, Fascicle 12, Washington DC, pp. 101-3.

2 **Abramson DH, Ellsworth RM, Kitchin FD, Tung G.** Second nonocular tumors in retinoblastoma survivors. Are they radiation induced? Ophthalmology 1984; 91: 1351-5.

3 **Francois J, de Sutter E, Coppieters R, de Bie S.** Late extraocular tumors in retinoblastoma survivors. Ophthalmologica 1980; 181: 93-9.

4 **Draper GJ, Sanders BM, Kingston JE.** Second primary neoplasms in patients with retinoblastoma. Br J Cancer 1986; 53: 661-71.

5 **Eng C, Li FP, Abramson DH, Ellsworth RM, Wong L, Goldman MB, Seddon J, Tarbell N, Boice Jr JD.** Mortality from second tumors among long-term survivor of retinoblastoma. J Nat Cancer Inst 1993; 85: 1121-8.

6 **Schifter S, Vendelbo L, Jensen OM, Kaae S.** Ewing's tumor following bilateral retinoblastoma. A case report. Cancer 1983; 51: 1746-9.

7 **Helton KJ, Fletcher BD, Kun LE, Jenkins JJ, Pratt CB.** Bone tumors other than osteosarcoma after retinoblastoma. Cancer 1993; 71: 2847-53.

8 **Albert LS, Sober AJ, Rhodes AR.** Cutaneous melanoma and bilateral retinoblastoma. J Am Acad Dermatol 1990; 23: 1001-4.

9 **Abramson DH, Ronner HJ, Ellsworth RM.** Second tumors in nonirradiated bilateral retinoblastoma. Am J Ophthalmol 1979; 87: 624-7.

10 **DerKinderen DJ, Koten JW, Nagelkerke NJD, Tan KEWP, Beemer FA, Den Otter W.** Non-ocular cancer in patients with hereditary retinoblastoma and their relatives. Int J Cancer 1988; 41: 499-504.

11 **Abramson DH, Ellsworth RM, Zimmerman LE.** Nonocular cancer in retinoblastoma survivors. Trans Am Acad Ophthalmol Otolaryngol 1976; 81: 454-7.

12 **Nuutinen J, Karja J, Sainio P.** Epithelial second malignant tumors in retinoblastoma survivors. A review and report of a case. Acta Ophthalmol Copenh 1982; 60: 133-40.

13 **Toguchida J, McGee T, Paterson JC, Eagle JR, Tucker S, Yandell DW, Dryja TP.** Complete genomic sequence of the human retinoblastoma susceptibility gene. Genomics 1993; 17: 535-43.

14 **Orita M, Iwahana H, Kanazawa H, Hayashi K, Sekiya T.** Detection of polymorphisms of human DNA by gel electrophoresis as single-strand conformation polymorphisms. Proc Natl Acad Sci USA 1989; 86: 2766-70.

15 **Lohmann DR, Brandt B, Höpping W, Passarge E, Horsthemke.** Distinct RB1 gene mutations with low penetrance in hereditary retinoblastoma. Hum Genet 1994; 94: 349-54.

16 **Orsouw N van, Li D, Vlies P van der, Scheffer H, Eng C, Buys CHCM, Li FP, Vijg J.** Mutational scanning of large genes by extensive PCR multiplexing and two-dimensional electrophoresis: application to the RB1 gene. Hum Mol Genet 1996; 5: 755-61.

17 **Enneking WF.** A staging system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

18 **Marcove RC, Stovell PB, Huvos AG, Bullough PG.** The use of Cryosurgery in the treatment of low and medium grade chondrosarcoma. Clin Orthop 1977; 122: 147-56.

19 **Marcove RC.** A 17-year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1987; 163: 231-4.

20 **Marcove RC, Sheth DS, Takemoto S, Healey JH.** The treatment of aneurysmal bone cyst. Clin Orthop 1995; 311: 157-63.

21 **Schreuder HWB, Veth RPH, Pruszczynski M, Lemmens JAM, Schraffordt Koops H, Molenaar WM.** Aneurysmal bone cysts treated by curettage, cryotherapy and bone grafting. J Bone Joint Surg (Br) 1997; 79: 20-5.

22 **Hugonnier R, Martin C, Vadot E, Pialat J, Roussille M.** Observation anatomo-clinique d'un sarcome radio-induit apres retinoblastome bilateral. Bull Soc Ophtalmol Fr 1987; 78: 31-2.

23 **Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W, Hoover RN, Fraumani JF.** Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 1987; 317: 588-93.

24 **Roarty JD, McLean IW, Zimmerman LE.** Incidence of second neoplasms in patients with bilateral retinoblastoma. Ophthalmology 1988; 95: 1583-7.

25 **Wunder JS, Czitrom AA, Kandel R, Andrulis IL.** Analysis of alterations in the retinoblastoma gene and tumor grade in bone and soft-tissue sarcomas.
J Natl Cancer Ins 1991; 83: 194-200.

26 **Reissmann PT, Simon MA, Lee WH, Slamon DJ.** Studies of the retinoblastoma gene in human sarcomas. Oncogene 1989; 4: 839-43.

27 **Stratton MR, Williams S, Fisher C, Ball A, Westbury G, Gusterson BA, Fletcher CD, Knight JC, Fung YK, Reeves BR, Cooper CS.** Structural alterations of the RB1 gene in human soft tissue tumors. Br J Cancer 1989; 60: 202-5.

28 **Wu Y, Hofstra RMW, Scheffer H, Uitterlinden AG, Mullaart E, Buys CHCM, Vijg J.**
Comprehensive and accurate mutation scanning of the CFTR-gene by two-dimensional DNA electrophoresis. Hum Mutation 1996; 8: 160-7.

29 **Nyström-Lahti M, Wu Y, Moisio AL, Hofstra RMW, Mecklin JP, Järvinen HJ, Leisti J, Buys CHCM, Chapelle A de la, Peltomäki P.** DNA mismatch repair gene mutations in 55 kindreds with verified or putative hereditary non-polyposis colon cancer.
Hum Mol Genet 1996; 5: 763-69.

CHAPTER 10

THE TREATMENT OF BENIGN AND LOW-GRADE MALIGNANT INTRAMEDULLARY CHONDROID TUMORS WITH CURETTAGE AND CRYOSURGERY

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ABSTRACT

Much controversy exists about the methods of evaluating, staging and final treatment of intramedullary chondroid lesions. This is particularly true for enchondroma and low-grade chondrosarcoma located in the extremities, because their accurate distinction is hampered by their radiographically and histologically similarity.
Since 1991 we treated 22 patients (mean age: 39.6 yrs) with 26 lesion (3 chondroblastomas, 14 enchondromas and 9 chondrosarcomas grade 1) with curettage, cryosurgery and bone grafting. The preoperative assessment of these lesions and cryosurgical technique is described in detail.
After a mean follow-up of 25 months no recurrences were observed. Complications consisted of two postoperative fractures, one wound infection and one intra-operative venous gas embolism. All bone grafts incorporated resulting in full-weightbearing capacity and excellent functional results.
The combination of curettage and cryosurgery as adjuvant therapy is considered to be equal as marginal resection according to orthopaedic oncologic principles.

INTRODUCTION

Intramedullary chondroid lesions of bone include chondroblastoma, chondromyxoid fibroma, enchondroma and chondrosarcoma. In general chondroblastoma, chondromyxoid fibroma and chondrosarcoma grade 2 and 3 do not pose major diagnostic problems. In contrast, the diagnostic distinction of enchondroma versus chondrosarcoma grade 1 is one of the most difficult areas

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patient	age (years)	gender	location of lesions	histology *		final staging	follow-up (months)	osteosyn-thesis	MSTS score	comments
				biopsy	resection					
1	45.1	M	tibia: prox. metaphysis	B	C	IA	34	plate	30	-
2	54.1	M	femur: diaphysis	B	C	IA	15	-	27	-
3	18.1	M	humerus: prox. metaphysis	D	D	3	34	-	30	-
4	44.0	F	5th metacarpal	A	A	3	40	-	30	-
5	38.1	F	femur: diaphysis	B	C	IA	30	-	28	fracture, developed 2nd primary chondrosarcoma grade 1 in scapula
6	36.5	M	humerus: prox. metaphysis	A	A	3	24	-	30	-
7	16.9	F	tibia: prox. epiphysis	D	D	3	32	-	28	-
8	48.4	F	tibia: dist. metaphysis	B	C	IA	34	-	30	breast carcinoma
9	65.5	F	fibula: prox. metaphysis	B	B	3	14	-	30	-
10	28.8	F	femur: prox. metaphysis	-	A	3	33	nail	30	bilateral retinoblastoma survivor all lesions in the right femur
			femur: dist. metaphysis	-	A	3				
			femur: diaphysis	C	C	IA				
11	47.3	M	femur: diaphysis	B	A	3	16	-	26	fracture
12	57.3	F	femur: distal metaphysis	B	B	3	27	-	30	-
13	20.5	F	femur: prox. metaphysis	A	A	3	25	-	30	Enchondromatosis; enchondroma rib, chondrosarcoma grade 1 ilium
14	50.1	M	digit 1: first phalanx	A	A	3	19	-	30	M. Ollier
			digit 2: first phalanx	A	A	3				
			fibula: prox. metaphysis	B	C	IA				
15	28.5	F	digit 4: first phalanx	A	A	3	37	-	30	-
16	34.1	F	femur: diaphysis	B	C	IA	37	plate	30	-
17	24.9	M	digit 2: first phalanx	A	A	3	20	-	30	-
18	27.5	M	trochanter major: epiphysis	D	D	3	14	-	30	-
19	56.5	F	femur: prox. metaphysis	B	C	IA	15	-	28	-
20	64.0	F	femur: prox. metaphysis	A	B	3	26	-	30	-
21	31.3	F	femur: diaphysis	B	C	IA	12	plate	30	-
22	35.3	F	digit 3: first phalanx	A	A	3	12	-	30	-

Table 10.1: A: enchondroma, B: enchondroma, chondrosarcoma grade 1 not excluded, C: chondrosarcoma grade 1, D: chondroblastoma.

of bone tumor pathology, where particularly close co-operation between pathologist, radiologist and orthopaedic surgeon is required.[1] These diagnostic problems are the result of poorly defined criteria and subjective interpretation of clinical, radiological and histological features of enchondroma and chondrosarcoma grade 1.[1-3] The continuous spectrum of biological behaviour of these entities is unpredictable and best illustrated by the fact that histological appearances of a cartilage tumor in the pelvis supporting the diagnosis of low-grade malignancy can be safely ignored when the lesion is located in the tubular bones of hands and feet.[1,4,5] The correct diagnosis may further be troubled by sampling errors; histologic features of enchondroma and chondrosarcoma may coexist in the same lesion.

It is established that a benign tumor as enchondroma can undergo malignant transformation into secondary chondrosarcoma,[3,6,7] especially in patients with multiple enchondromas as in Ollier disease and Maffuci syndrome.[8]

Difficulty in diagnosis, potential malignancy, under and overdiagnosis may lead to uncertainty concerning the necessary treatment and the optimal extent of surgery. Because of low recurrence risk of enchondroma and low-grade chondrosarcoma in extremities, limited surgery with or without adjuvant therapy is advocated.[9-11]Since 1991, in our institution chondroblastoma, enchondroma and intramedullary low-grade chondrosarcoma are treated by intralesional resection, cryosurgery and bone grafting, originally described by Marcove.[12] This paper emphasizes on our methods of evaluation and technique of treating these tumors and we evaluate results, complications and functional outcome.

METHODS AND PATIENTS

We conducted a study of patients with an intramedullary benign, stage 2 and 3 or low-grade malignant, stage IA chondroid tumor located in the extremity.[13] Only patients with a minimal follow-up of 12 months or more are included in this study, leaving 22 patients with 26 lesions (two patients had three lesions). There were 8 males and 14 females, mean age: 39.7 (range: 16.9-65.5).

At presentation a standard work-up was carried out. This included; history, physical examination, radiographs, total body bone scan, magnetic resonance imaging, biopsy, definite surgical treatment and protocolized follow-up.

Biopsy. Biopsy is carried out using an image intensifier to locate the most suspicious part of the lesion (lucent areas) and to document the exact location of the site biopsized. A trochar system capable of taking a sample consisting of cortex, intramedullary tissue and tumor was used. Usually cylindrical samples with a diameter of 5 mm and a length of one cm or more could be obtained. The biopsy should be made in such a way that it will not compromise any possible approach later utilized for definite treatment.

Radiographic evaluation: On plain radiography chondroblastoma appears as an oval or rounded, smoothly marginated, well-defined lucency with a thin, peripheral reactive osseous rim,[14] usually situated in the apophysis of bone.

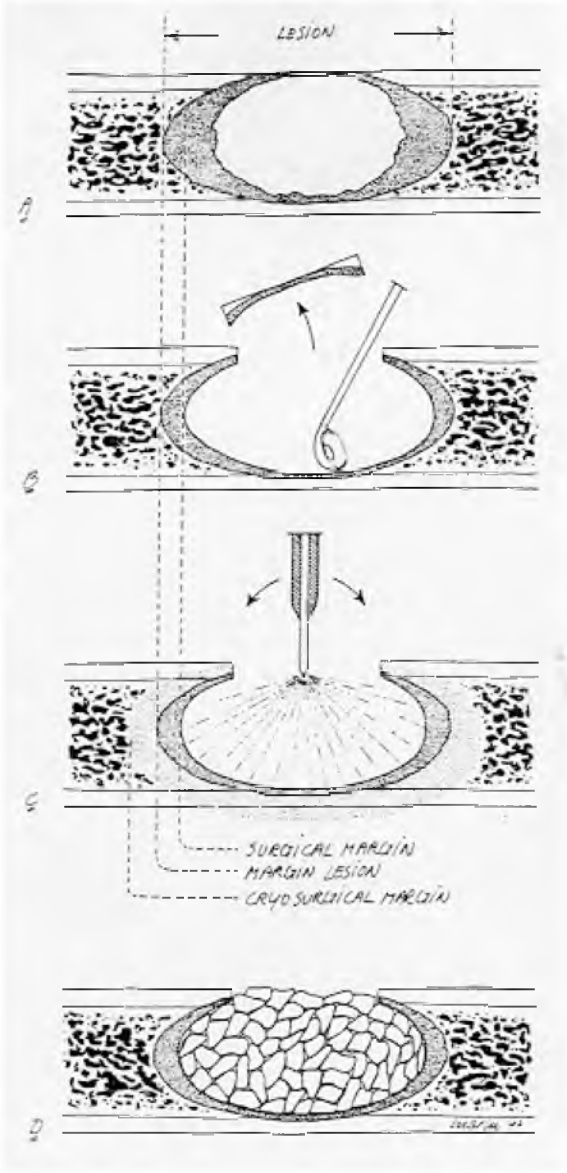

Figure 10.1: The lesion in figure 1 is curetted resulting in a surgical margin (B), the spraying of liquid nitrogen (C) will result in an additional thermal injury inducing tissue necrosis extending beyond the borders of the lesion: the cryosurgical margin. The bony cavity is filled with a bone graft (D).

Chondroblastoma may break through the cortex and invade a joint or adjacent soft tissues, which all can be assessed with CT and MRI.[14]
Enchondroma and low-grade chondrosarcoma are usually located centrally in the metadiaphysis. Enchondroma appears as a oval lesion with a cartilaginous matrix mineralization including punctate, flocculent, or rings and arcs[15] calcifications. In a narrow bone (hand) enchondroma frequently involves the entire width, causing expansion of the affected bone. Intramedullary low-grade chondrosarcoma has in addition to the features of enchondroma frequently lytic area(s) interspersed within the lesion. The cortex adjacent is often thinned (scalloping) or violated.[16]
CT detects both subtle matrix mineralization and the integrity of the adjacent cortex, MRI is best for judging the extent of the lesion and these modalities will help in the radiographic distinction of enchondroma versus low-grade chondrosarcoma.[17,18]
Surgical technique. Standard orthopaedic oncologic exposures are used. When the exact location of a lesion or the proximity of a growth plate is unclear, an image intensifier is used. To avoid inadvertent freezing of the skin, wide retraction is mandatory. We never use extremity tourniquets, because normal circulation decreases the risk of freezing nearby neurovascular bundles and skin.Normally it is not necessary to dissect the neurovascular bundle away from the lesion to be frozen.
A sufficient oval window is made in the cortex using a drill or saw. The tumor is resected as thoroughly as possible using a curette (Figure 10.1B). Care is taken to avoid pushing tumor into the uninvolved medullary canal.
To monitor the intralesional temperature and local extent of the freeze, thermocouples are positioned in and around the lesion. A thermocouple placed adjacent to the neurovascular bundle will prevent inadvertent freezing by stopping the spraying of liquid nitrogen in time. Temperature data acquisition is done using a digital multimeter equipped with a thermocouple scanner card. Graphical real-time visualization of the course of the temperatures is done by connecting the multimeter to a personal computer (Chapter 11).
Cryosurgery is then performed (Figure 10.1C). Three cycles of cryosurgery are performed using a machine producing a liquid nitrogen spray (ERBOKRYO NL, ERBE, Nieuwegein, The Netherlands). This spray is directed in the lesion in every direction, until the whole cavity is wetted and becomes frosted. The nitrogen vapor, clouding the view is waved away by hand. The duration of each freeze is based on the temperature readings and visual observation. Intralesional temperatures of at least -50°C are pursued and necessary to induce tissue necrosis.[19,20] Warming up until 20°C is done by spontaneous thawing.
Following the cryosurgery the entire wound and cavity is "washed" with sodium hypo-nitrate to prevent seeding of tumor cells.
The defect remaining after curettage and cryosurgery is filled with autograft or allograft bone chips. The cortical window is frozen as well and is replaced or used as a source of bone graft (Figure 10.1D).
A careful soft tissue reconstruction is very important, restoring the periosteum, if possible and covering the bone with muscle. A wound drain is always used and

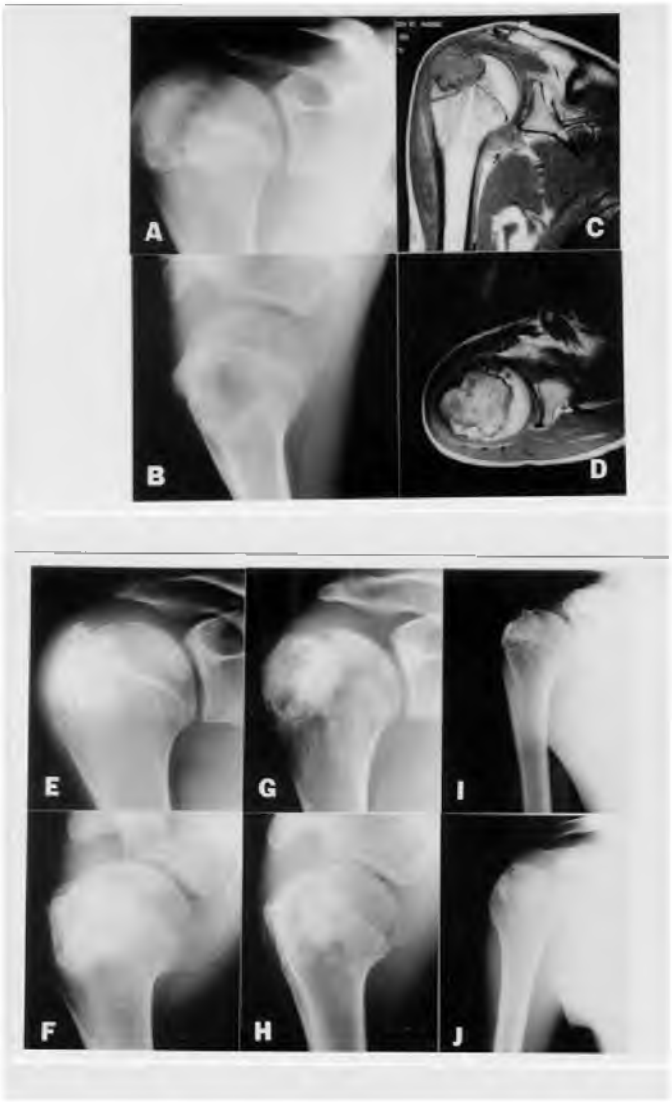

Figure 10.2: Routine radiographs of chondroblastoma (patient 3, table 10.1) located in proximal epiphysis of humerus (A,B). The lesion was painful, because of pathologic, minimal displaced fracture of tuberculum majus. T1 weighted MRI studies, the extent of the lesion is accurately depicted (C=coronal, D=transversal). Three (E,F), eight (G,H) and 30 months after curettage, cryosurgery and homologous bone grafting. Progressive incorporation and remodelling of the graft, resulting in nearly normal bone structure at latest follow-up. No evidence of recurrence. Normal, pain free function.

it should only be removed when drainage falls below 30 ml per 24 hours. Peri-operative antibiotics are routinely used. If the strength of weightbearing bones, in particular the diaphysis of the femur, is compromised by the lesion and cryosurgery, prophylactic internal fixation is advised, using a plate and screws. An intramedullary enforcement is ill advised, because it has the risk of contaminating the entire intramedullary compartment with tumor cells. Partial weightbearing is usually necessary until three months after the operation.

Histology. The histological diagnosis of chondrosarcoma grade 1 was made only when next to the cytological features an evident chondrosarcomatous pattern was present. This pattern shows hyaline or myxoid cartilage permeating lamellar bone (chondrosarcoma permeation pattern) replacing marrow fat (invasion of marrow fat pattern), bands of fibrosis and infiltration of Haversian system.[3] The histological diagnosis had to be concurrent with the clinical and radiographical picture.

Follow-up. All patients had protocolized follow-up. Functional assessment was performed at the most recent follow-up visit and consisted of operation-related complaints and physical examination and scored according to the system for functional evaluation of surgical management of musculoskeletal tumors.[21]

RESULTS

Age and gender of the patients, the anatomical distribution, histological diagnosis of biopsy and subsequent resected material and final staging are shown in Table 10.1. After definite treatment 17 lesions were staged as 3 (aggressive benign) and 9 as IA (low-grade malignant, intra-compartmental). Comparing histology results of biopsy versus resection, eight enchondroma were "upgraded" to a histology with preference for chondrosarcoma grade 1.

After a mean follow-up of 25 months (range: 12-40) none of the patients showed any evidence of a recurrence.

Two patients sustained postoperative pathological fracture (patients 5 and 11 in Table 1), both successfully healed with conservative treatment. One of them (patient number 5) had also a wound infection, which resolved after prolonged use of antibiotics. One patient suffered a venous gas embolism, which was noted because of hemodynamic instability during cryosurgery, without permanent damage. No neuro-vascular complications were experienced.

All bone grafts incorporated and remodelled resulting in full-weightbearing capacity in all patients (Figure 10.2, 10.3 and 10.4).

The mean MSTS score was 29.4 points (range: 26-30). All patients had excellent functional results and resumed their preoperative status of daily activities.

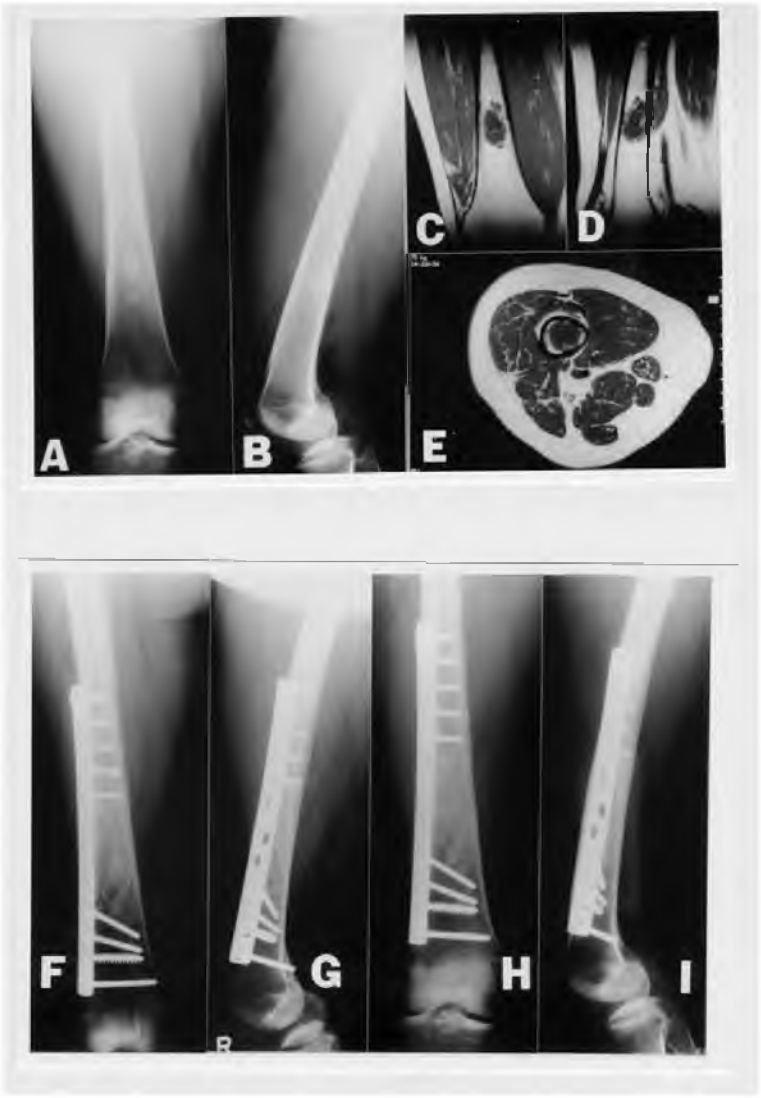

Figure 10.3: Routine radiographs (A,B) of symptomatic enchondroma in diaphysis of femur (patient 16, table 10.1). T1 weighted MRI: coronal (C) and sagittal (D). On transversal (E) view some endosteal reaction is seen. Two (F,G) and 37 (H,I) months after curettage, cryosurgery and homologous bone graft. No evidence for recurrence.

DISCUSSION

Much controversy exists about the methods of evaluating, staging and final treatment of an intramedullary chondroid lesion and this particular topic remains open for discussion. The reason for this controversy is partly due to the lack of hard criteria creating the possibility of differentiating radiologically benign enchondroma from low-grade chondrosarcoma. Furthermore, the histologic picture of benign enchondroma and chondrosarcoma grade 1 shows in more than 25% of the cases complete overlapping concerning nuclear atypia, cellularity and number of double-nucleated cells, thus, the accurate distinction between enchondroma and well-differentiated chondrosarcoma is seriously hampered by their cytologic similarity[3]. The combined cytologic and histologic approach suggested by *Sanerkin,*[22] later refined by *Mirra et al*[3] to differentiate enchondroma versus low-grade chondrosarcoma has generally been adopted. It consists of pathohistologic characterizations distinguishing an enchondromatous pattern with "islands of cartilage" (islands of cartilage pattern) that are partially or completely surrounded by plates of lamellar bone and bone marrow (enchondroma encasement pattern "EEP") from a chondrosarcomatous pattern where hyaline or myxoid cartilage permeates lamellar bone (chondrosarcoma permeation pattern), replaces marrow fat (invasion of marrow fat pattern) and bands of fibrosis and infiltration of the Haversian system are seen.

Cytogenetic studies have not show a correlation between histological grade and chromosomal pattern of chondrosarcoma.[23] Investigation of collagen types in the extracellular matrix of chondroid lesions showed alterations of collagen distribution to more immature types of collagen in low-grade chondrosarcoma.[24]

In view of the diagnostic difficulties of chondroid lesions, generous material for biopsy is mandatory, and the use of clinical and radiographical evidence is critical to formulate the correct histological diagnosis.[25]

Concerning the treatment advised for benign, stage 3, enchondroma and low-grade chondrosarcoma, stage IA no consensus of opinion exists. *Bauer et al* concluded after a study of 40 patients with enchondroma and 40 with low-grade chondrosarcoma that limited surgery (curettage) is indicated because of low recurrence rates, respectively 0.04% and 0.09%.[9] On the other hand *Tsuchiya et al* advises wide excision of borderline chondrosarcoma, in the same manner as low-grade chondrosarcoma.[24] *Sanerkin et al* found that low-grade chondrosarcoma had a 5 year survival rate of 89%. Local recurrence rate was 85%, strongly influenced by inadequate treatment, which was defined as resection with contaminated margins.[26]

Enneking states that enchondroma treated with curettage has a substantial recurrence rate and tend to extend beyond the margins of the original lesion. Recurrence after marginal excision is very low and nil after wide en block resection. However, he finds that in many clinical situations, these more aggressive procedures may produce a functional defect that is unacceptable considering the innocence of the disease. Clinical prudence frequently suggests an observational course following the diagnostic impression of enchondroma.[27]

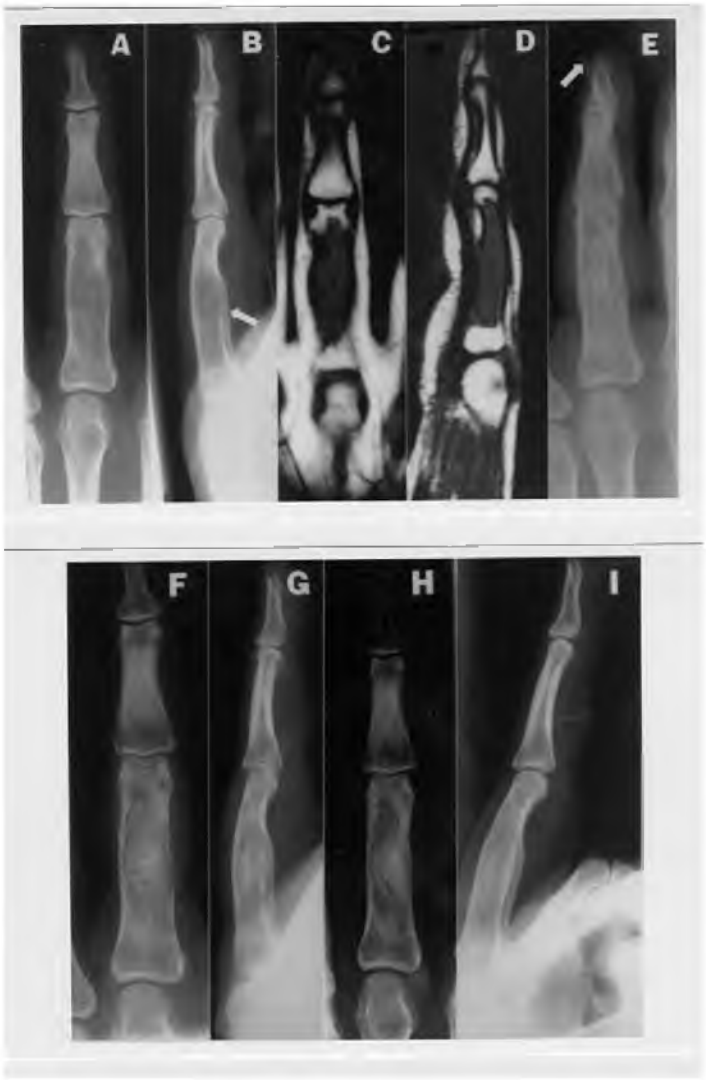

Figure 10.4: Radiographs of painful enchondroma (A,B) located in first phalanx of digit 3 (patient 21, table 10.1). Periosteal reaction (arrow). T1 weighted MRI: coronal (C) and sagittal (D). Post-operative view after curettage, cryosurgery and autologous bone graft, wound drain in situ (arrow). Seven weeks (F,G) and 12 months (H,I) postoperatively, progressive incorporation of bone graft, normal function.

Campanacci advises treatment consisting of curettage, phenol and bone graft, only when enchondroma is symptomatic (pain) and have osteolytic areas on radiographs.[28] For borderline cases of enchondroma versus low-grade chondrosarcoma aggressive intralesional resection followed by adjuvant treatment with phenol, cement or cryosurgery is allowed. All other forms of chondrosarcoma need resection with adequate margins.[29]

Since biopsy may understate enchondroma and low-grade chondrosarcoma IA with hard to predict biological courses and histological diagnostic problems, it is our opinion that these lesions should be treated by marginal resection. Because this would imply en block resections in most cases with the associated morbidity and technical difficulties of reconstruction, we adopted the technique of curettage with adjuvant cryosurgery, which together is considered as marginal according to orthopaedic oncologic principles.[13] The efficacy of this treatment has been shown for other skeletal lesions.[30-33] In our series of patients with a mean follow-up of 25 months we found no recurrences. For these specific type of tumors this follow-up period is short and our results may be classified as preliminary.

REFERENCES

1 **Reid R.** New developments in the diagnosis of chondrosarcoma. J Pathol 1991; 163: 93-4.

2 **Meachim G.** Histological grading of chondrosarcomata. J Bone Joint Surg (Br) 1979; 61: 4-5.

3 **Mirra JM, Gold R, Downs J, Eckardt JJ.** A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orthop 1985; 201: 214-37.

4 **Giudici MA, Moser RP Jr, Kransdorf MJ.** Cartilagious bone tumors. Radiol Clin North Am 1993; 31: 237-59.

5 **Bresser E, Roessner A, Brugg E, Erlemann R, Timm C, Grundman E.** Bone tumors of the hand. A review of 300 cases documented in the Westphalian Bone Tumor Register. Arch Orthop Trauma Surg 1987; 106: 241-7.

6 **Marcove RC.** Chondrosarcoma: diagnosis and treatment. Orthop Clin North America 1977; 8: 811-20.

7 **Healey JH, Lane JM.** Chondrosarcoma. Clin Orthop 1986; 204: 119-29.

8 **Schwartz HS, Zimmerman HB, Simon MA, Wroble RR, Millar EA, Bonfiglio M.** The malignant potential of enchondromatosis. J Bone Joint Surg (Am) 1987; 69: 269-74.

9 **Bauer HCF, Brosjö O, Kreicbergs A, Lindholm J.** Low risk of recurrence of enchondroma and low-grade chondrosarcoma in extremities. 80 patients followed for 2-25 years. Acta Orthop Scand 1995; 66: 283-8.

10 **Quint U, Pingsmann A.** Surgical treatment of enchondroma in long tubular bones. Preservation of function versus extensive excision in the humerus. Arch Orthop Trauma Surg 1995; 114: 352-6.

11 **Eriksson AI, Schiller A, Mankin HJ.** The management of chondrosarcoma of bone. Clin Orthop 1980; 153: 44-66.

12 **Marcove RC, Stovell PB, Huvos AG and Bullough PG.** The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. A preliminary report. Clin Orthop 1977; 122: 147-56.

13 **Enneking WF.** A staging system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

14 **Mandell GA, Harcke HT, Kumar SJ.** Chondroid lesions of the extremities. Top Magn Reson Imaging 1991; 4: 56-65.

15 **Aoki J, Sone S, Fujioka F, Terayama K, Ishii K, Karakida O, Imai S, Sakai F, Imai Y.** MR of enchondroma and chondrosarcoma: rings and arcs of Gd-DTPA enhancement. J Comput Assist Tomogr 1991; 15: 1011-6.
16 **Lodwick GS.** The radiologist's role in the management of chondrosarcoma. Radiology 1984; 150: 275.
17 **Giudici MA, Moser RP Jr, Kransdorf MJ.** Cartilagious bone tumors. Radiol Clin North Am 1993; 31: 237-59.
18 **De Beuckeleer LH, De Schepper AM, Ramon F.** Magnetic resonance imaging of cartilaginou s tumors: is it useful or necessary? Skeletal Radiol 1996; 25: 137-41.
19 **Gage AA.** What temperature is lethal for cells? J Dermatol Surg Oncol 1979; 5: 459-60.
20 **Gage AA, Guest K, Montes M, Caruana JA and Whalen Jr DA.** Effect of varying freezing an d thawing rates in experimental cryosurgery. Cryobiology 1985; 22: 175-82.
21 **Enneking WF, Dunham W, Gebhardt MC et al** A system for the functional evaluation o f reconstructive procedures after surgical treatment of tumors of the musculoskeletal systems. Clin Orthop 1993; 286: 241-46.
22 **Sanerkin NG.** The diagnosis and grading of chondrosarcoma of bone: a combined cytologic an d histologic approach. Cancer 1980; 45: 582-94.
23 **Dijkhuizen T, van den Berg E, Molenaar WM, Oosterhuis JW, Dam A, Wiersema J, Schraffordt Koops J and de Jong B.** Cytogenetics as a tool in the histologic subclassification o f chondrosarcomas. Cancer Genet Cytogenet 1994; 76: 100-5.
24 **Tsuchiya H, Ueda Y, Morishita H, Nonomura A, Kawashima A, Fellinger EJ, Tomita K.** Borderline chondrosarcoma of long and flat bones. J Cancer Res Clin Oncol 1993; 119: 363-8.
25 **Unni KK.** Dahlin's bone tumors: general aspects and data on 11,087 cases. Fifth ed. Philadelphia: Lippincott-Raven, 1996: 84.
26 **Sanerkin NG and Gallagher P.** A review of the behaviour of chondrosarcoma of bone. J Bone Joint Surg (Br) 1979; 61-B: 395-400.
27 **Enneking WF.** Musculoskeletal tumor surgery. Vol. 2, Edingburgh: Churchill-Livingstone, 1993: 883.
28 **Campancci M.** Bone and soft tissue tumors. New York: Springer-Verlag, 1996: 223.
29 **Campancci M.** Bone and soft tissue tumors. New York: Springer-Verlag, 1996: 300-1.
30 **Marcove RC, Stovell PB, Huvos AG, Bullough PG.** The use of Cryosurgery in the treatment of lo w and medium grade chondrosarcoma. Clin Orthop 1977; 122: 147-56.
31 **Marcove RC.** A 17-year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1987; 163: 231-4.
32 **Marcove RC, Sheth DS, Takemoto S, Healey JH.** The treatment of aneurysmal bone cyst. Clin Orthop 1995; 311: 157-63.
33 **Schreuder HWB, Veth RPH, Pruszczynski M, Lemmens JAM, Schraffordt Koops H, Molenaar WM.** Aneurysmal bone cysts treated by curettage, cryotherapy and bone grafting. J Bone Joint Surg (Br) 1997; 79: 20-5.

CHAPTER 11

MONITORING DURING CRYOSURGERY OF BONE TUMORS*

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ABSTRACT

Background: Cryosurgery is used in orthopaedic oncology as adjuvant treatment after intralesional resection of bone tumors to induce cell death at and beyond the surgical margin. Monitoring freeze/thaw cycles during cryosurgery is beneficial in controlling a cryosurgical procedure and in preventing an unwarranted local extent of the freeze.
Method: We conducted a study of 15 cryosurgical procedures with the use of a protocolized temperature measuring system with peroperative graphic visualization.
Results: Using a liquid nitrogen spray, intralesional temperatures of -150°C were achieved, which are, according to the literature, associated with cell death. Extralesional temperature measurements showed no subzero temperatures of surrounding important tissues.
Conclusions: Temperature recordings in and outside the lesion during cryosurgery in orthopaedic oncology are of importance to monitor the freeze/thaw cycles and are helpful in facilitating an effective cryosurgical procedure and in controlling the extent of the freeze, avoiding local complications.

INTRODUCTION

Cryosurgery utilizing liquid nitrogen is practiced in orthopaedic oncology for the treatment of primary benign and malignant bone tumors as well as for secondary metastases to bone. In benign and low-grade malignant stage IA skeletal tumors[1] it is used as an adjuvant treatment to intralesional resection (curettage) to extend the surgical margin of resection.[2-10] By this method the procedure can be considered to be marginal according to oncologic principles.[1] The advantage of this kind of treatment, as compared to local resection, is that as much as possible

of the supportive function of bone is preserved and that reconstructive surgery can be limited.
In high grade sarcomas, cryosurgery has been used as the primary treatment with variable results.[10,11] Cryosurgery used in the treatment of bony metastases has to be considered as palliative and in this respect helpful in local control of the malignancy.[12,13]
Since the introduction of cryosurgery in medicine, monitoring modalities have been developed to visualize the local process for the following reasons:

A. To ensure that lethal temperatures for tumor cell death are reached. The temperature of frozen tissue cannot be determined by its visual appearance alone, since frosted tissue looks the same at any freezing temperature.[14,15]
B. An accurate measurement of the depth and lateral spread of the freeze is necessary, not only for obtaining adequate margins, but also to avoid an unwarranted extension of the freezing inducing potential morbidity.[15]
C. Local temperature measurement enables a more precise determination of the ending of the thawing phase. Complete spontaneous warming up of the frozen tissue before the next freeze/thaw cycle is started is important to induce a maximum lethal effect on tumor cells.[16]
D. Monitoring, and preferably recording of the cryosurgical procedure, enables the physician to evaluate the procedure itself and interpret follow-up results with respect to the procedure. Adjustments in technique can be developed and introduced. Scientific research on recorded data will ultimately improve the quality of cryosurgery.
E. Recording of the whole freezing procedure provides written evidence, which may be of medicolegal importance.

Next to local monitoring, systemic monitoring seems to be of importance, because whenever a gas is introduced into a body cavity, there is always the hazard of intravascular introduction of gas bubbles. Gas emboli in the vascular circulation can cause serious hemodynamic complications and has been associated with potentially lethal circulatory and pulmonary complications.[17-19] Cryosurgery of bone tumors is in this perspective no exception and has been associated with (lethal) complications in the past.[20,21]
This report describes the technical details and results of local monitoring with thermocouples during cryosurgery of bone tumors (Figure 11.1A-D, 11.2A-D).

MATERIALS AND METHODS

For the local monitoring of cryosurgery of bone tumors, we developed a multifocal temperature measuring system utilizing up to nine thermocouples. The thermocouples consist of a copper/copper-nickel alloy and are mounted in the

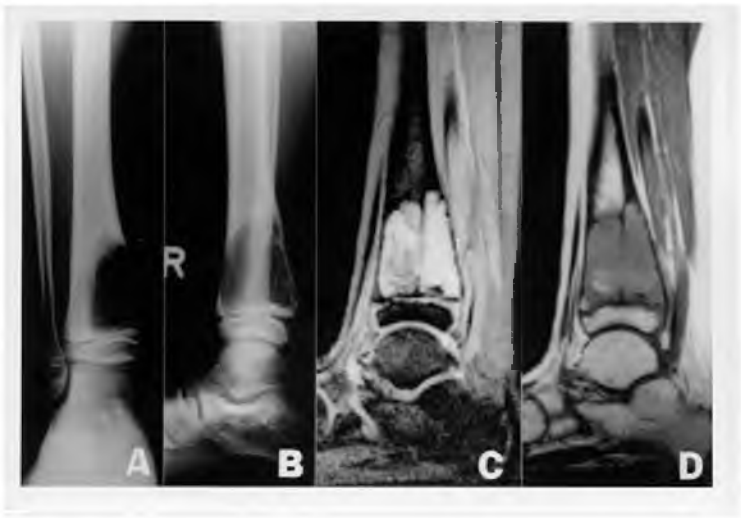

Figure 11.1 A,B,C and D: Routine radiographs of an 11-yr.-old boy with aneurysmal bone cyst in the distal tibia, very close to the growthplate (A,B). Magnetic resonance imaging, T2 (C) and T1 (D), showing erosion of cortex and a fairly homogenous intensity of the contents of the cyst consistent with fluid.

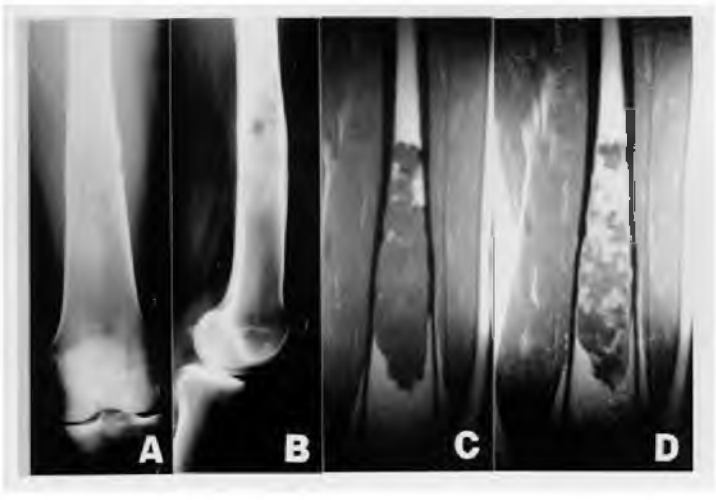

Figure 11.2 A,B,C and D: Postbiopsy routine radiographs of a 29yr.-old female with chondrosarcoma, grade 1 of diaphysis of diaphysis of the femur (A,B). Magnetic resonance imaging, T1 (C) and T2 (D) weighed showing erosion of cortex and an inhomogeneous signal intensity consistent with enchondroma or low-grade chondrosarcoma.

tip of a 50-mm-long and 0.8-mm-diameter injection-like needle (Ellab A/S; Roedovre, Denmark). Their accuracy is better than 0.1°C with a response time of 0.3 s. Temperature data acquisition was done using a digital multimeter (Digital multimeter 2000, Keithley Instruments, Cleveland, OH) equipped with a thermocouple scanner card (2001-TCSCAN, Keithley Instruments). Graphical real-time visualization of the course of the temperatures is accomplished by connecting the multimeter to a personal computer running appropriate "homemade" software. Next to performing real-time display, this program stores all temperature data for later analysis.

After exposure of the tumor, bony fenestration is performed followed by intralesional resection (curettage) of the tumor. Thermocouples are placed according to a fixed protocol: two to monitor the axial intramedullary spread of the freeze, respectively, proximal and distal of the lesion and two or more extracortical, around the lesion to monitor the lateral spread of the freeze. One thermocouple is situated in the lesion itself and reflects the intralesional surface temperature. Additional thermocouples can be used adjacent to structures that should not be damaged, such as neurovascular bundles and growth plates, or in joints to prevent damage of the articular cartilage. Intraoperative radiographs are used to document the location of the thermocouples more precisely (Figure 11.1E,F and 11.2E,F).

Three cycles of cryosurgery are performed using a machine producing a liquid nitrogen spray (ERBOKRYO NL, ERBE, Nieuwegein, The Netherlands). The duration of each freeze is based on the temperature readings and visual observation. Warming up is done by spontaneous thawing. Reconstruction of the bony defect is carried out with an autologous and/or homologous bone graft (Figure 11.1G,H and 11.2G,H).

The protocolized temperature measurement system was used in 15 patients (5 females, 10 males) with a mean age of 31.7 yrs (range 11-64), all having active or aggressive benign lesions,[1] which are specified in Table 11.1.

Location/diagnosis	humerus	pelvis	femur	tibia	radius	total
GCT	1		1		2	4
ABC		1		1		2
SBC	3			1		4
chondroblastoma	1		1			2
enchondroma			3			3
Total:	**5**	**1**	**5**	**2**	**2**	**15**

Table 11.1: Anatomical distribution and diagnosis of 15 skeletal tumors treated with curettage, cryosurgery and bone grafting (GCT=giant cell tumor, ABC=aneurysmal bone cyst, SBC=simple bone cyst).

RESULTS

Every patient had almost similar temperature recordings during their three freeze-thaw cycles. Two typical examples are shown in Figure 11.3A and 11.3B. In all cases the intralesional recording, which reflects the surface temperature of the bony cavity reaches -50°C in a mean time of 10.6 s (range: 8-15s) after the spraying with liquid nitrogen is started. A temperature of -150°C and below was easily achieved in all cases, with the exception of two giant cell tumors of the distal radius. Continuous spraying for 15-20 s resulted in an intralesional temperature of -50°C or below during a mean of 39.3 s (range: 22-88s). Spontaneous thawing between -50° and 0°C took on the average 152.6 s (range: 30-420s). In this period the increasing temperature frequently entered a subzero plateaux phase varying in time from 20 s to 250s. Thawing from 0 to 20°C required in general 290 s (range: 90 to 900s). In Table 11.2 these monitoring readings are specified for, respectively, the first, second and third cycles.
Thermocouples monitoring the axial and lateral spread of the freeze showed a delayed temperature decrease but it almost never dropped below 0°C.
The temperature recorded by the extracortical thermocouples, which are only separated from the freeze by the thickness of the cortex, sometimes declined just below 0°.
In general the whole area around the frozen lesion cooled down lengthening the time needed for thawing to 20°C after every freeze (Figure 11.3A,B).

Temperature phase	**37°C -> -50°C**			**-50°C and lower**			**-50°C -> 0°C**			**0°C -> 20°C**		
Cycle	1	2	3	1	2	3	1	2	3	1	2	3
Mean time cycle (s)	9.5	11.5	10.7	40.1	36.0	41.7	136.8	165.0	156.0	221.7	294.3	354.0
Mean time 3 cycles (s)	10.6			39.3			152.6			290.0		

Table 11.2 Temperature monitorings of 15 cryosurgical procedures included in this study. Mean time o f temperature phase per cycle (1,2 or 3) and of all 3 cycles (C=celsius, s=second).

DISCUSSION

The common practice of monitoring a cryosurgical procedure guided by the physician's clinical judgment and experience is found particularly in freezing *soft* tissue lesions. The progress of the treatment can be followed by observation and palpation, and the depth of freezing can be estimated by observing the lateral spread of freezing in the target tissue.[15,22] Although clinical judgment of freezing extent is reasonably accurate, it is probably not enough to perform a controlled cryosurgical procedure when tissues with different thermal characteristics are involved. In orthopaedic oncology, these are cortical bone, intramedullary spongiosa, and soft tissues mainly muscle. To supplement clinical judgment

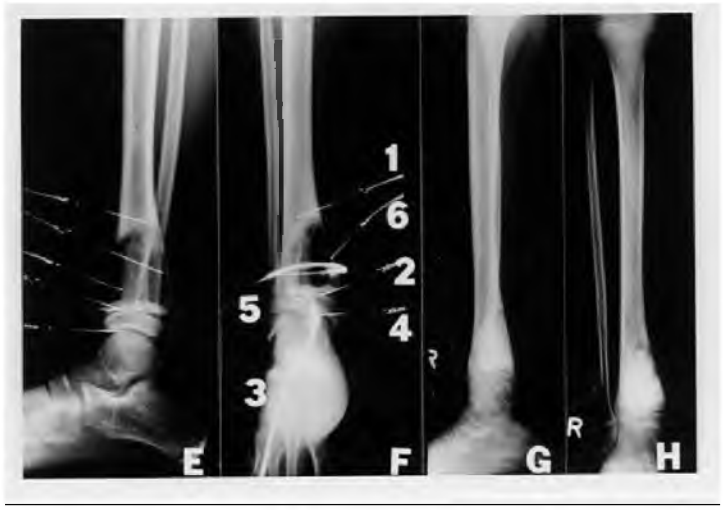

Figure 11.1 E,F,F and H: Intraoperative radiographs showing localization of the temperatur e couples. Number 2 and 3 are situated in the growthplate, number 4 is intra-articular (E,F). Th e intralesional temperature couple, number 7 was added later. Numbers correspond with those i n Figure 11.3A. After curettage and cryosurgery the cyst is filled with a homologous bone graf t (G,H).

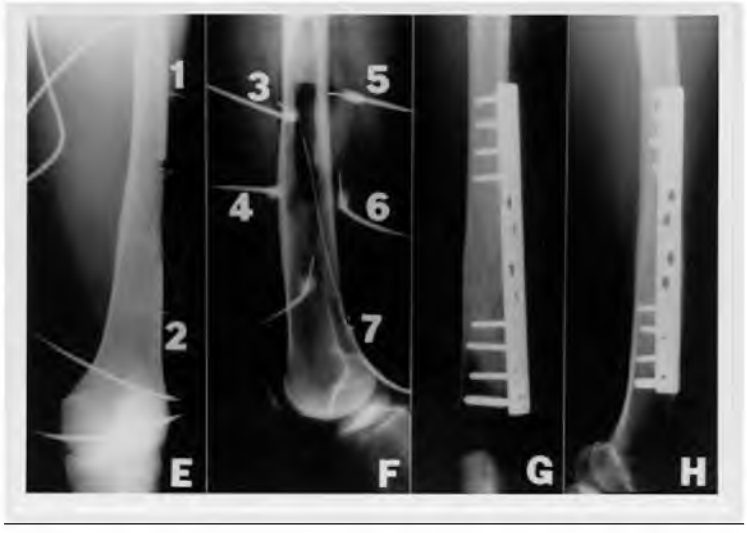

Figure 11.2 E,F,G and H: Intra-operative radiographs showing localization of the temperatur e couples. Number 7 is situated in the curetted lesion. Numbers correspond with those in Figur e 11.3B (E,F). After curettage and cryosurgery the cyst is filled with a homologous bone graft (G,H).

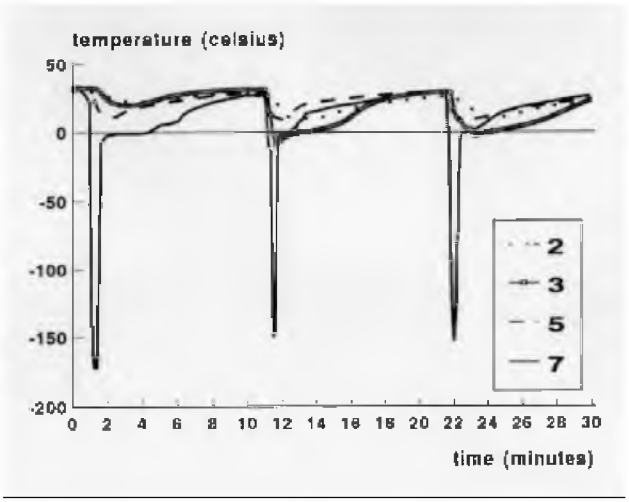

Figure 11.3A: Temperature recordings of patient in Figure 11.1; numbers correspond with those in Figure 11.1E,F. The temperature measured by the thermocouples 1,4 and 6 were at all time s above 25°C. For reasons of clarity of the graph they are not shown.

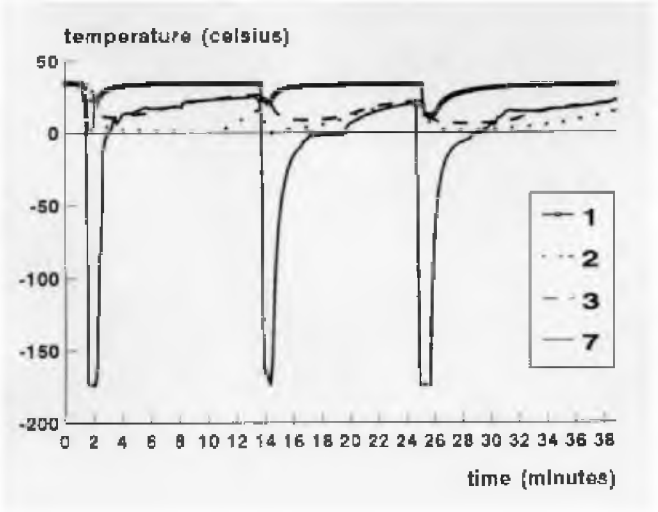

Figure 11.3B: Temperature recordings of patient in Figure 11.2; numbers correspond with those in Figure 11.2E,F. The temperature measured by the thermocouples 4,5 and 6 were at all time s above 10°C. For reasons of clarity of the graph they are not shown.

during cryosurgery, a range of monitoring devices and techniques has been developed, most to address monitoring needs for specific applications of cryosurgery. Measurement modalities are thermography,[23] which involves very expensive equipment and provides only surface freezing evaluation),[15] ultrasound,[24,25] which is not suitable for bony tissue, and tissue impedance and resistance measurements,[26-28] which causes concern about accuracy.[16]
Computerized tomography[29] and magnetic resonance[30-32] are capable of visualizing frozen tissue, but their high cost and the logistics involved make them unsuitable for the orthopaedic setting. In this perspective we developed our system using temperature couples.
Thermocouples were first used to monitor cryosurgery of skin lesions. Their importance was recognized early in cryosurgical practice, particularly in establishing lethal temperatures.[33]
Using the temperature measuring system with real-time graphical visualization, we showed that with this freezing technique, intralesional temperatures of -150°C are achieved within seconds (freezing-rate > $10°C.s^{-1}$). Furthermore, the maintenance of a temperature of -50°C for 40 s, the apparent holding of this low temperature and the tissue in frozen state for 3 min, followed by spontaneous slow thawing and repetition of freeze/thaw cycles are all of importance to maximize tissue destruction.[16,34]
Using extralesional thermocouples we were able to show that important structures were not subjected to subzero, potentially damaging temperatures. Furthermore extralesional thermocouples enable the surgeon to optimize the duration and lateral spread of the freeze.
Extremely high freezing rates by spraying liquid nitrogen are achieved. These rates are associated with intracellular formation of ice crystals, inducing mechanical damage to the cell and thus cell death.[34-38]
After spraying has been stopped and thawing is allowed, the extralesional thermocouples show a further lowering of temperature, representing the retraction of tissue heat, which is used for the thawing of the more central parts of the frozen lesion. The nonlinear increase of the temperature in frozen tissue and its subzero plateau phase is explained by additional energy needed for the transition of ice into water, which halts the temperature increase temporarily.
Figure 11.3 shows an almost identical pattern of the freeze/thaw cycles, indicating cryosurgery utilizing a spray is a reproducible method.
The accuracy of the thermocouple readings is important as the effectiveness of treatment partially depends on it. Proper calibration and reliable hardware (good quality of thermocouple, wiring, electrical connections, and display devices) are imperative. Even more critical is the correct placement of the thermocouple itself: a 1 mm variation in the thermocouple positioning can represent a 10-15°C temperature difference.[39]
In addition to routine systemic monitoring of the patient, end-tidal gas analysis is performed using a mass spectrometer measuring inspired and end-tidal O_2, CO_2, N_2O, N_2 tensions and anesthetic vapor concentration. Using real-time recording of the gas analysis breath by breath makes detection of any exhaled N_2 possible,

which is associated with venous nitrogen gas embolism. In this way, we hope to take appropriate action in time to prevent serious hemodynamic complications. Because we had cardiopulmonary complications in two patients, as reported earlier,[21] we started to monitor our patients with peroperative transesophageal ultrasound of the heart. Using this method in five cases, we did not detect any venous gas embolisms during our cryosurgical procedures.

We conclude that temperature recordings in and outside the lesion during cryosurgery in orthopaedic oncology are of importance to monitor the freeze/thaw cycles and are very helpful in facilitating an effective, reproducible cryosurgical procedure and in controlling the extent of the freeze avoiding local complications. Systemic monitoring is of paramount significance for the safety of the patient.

REFERENCES

1 **Enneking WF.** A staging system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

2 **Malawer MM and Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in th e treatment of aggressive (benign) bone tumors. Clin Orthop 1991; 262: 42-57.

3 **Oeseburg HB, Rogge CWL, Schraffordt Koops H and Oldhoff J.**Cryosurgical treatment o f aneurysmal bone cysts. J Surg Oncol 1978; 10: 9-20.

4 **Gage AA and Erickson RB.**Cryotherapy and curettage for bone tumors. J Cryotherapy 1968; 1: 60-6.

5 **Marcove RC, Lyden JP, Huvos AG and Bullough PG.**Giant cell tumors treated by cryosurgery. A report of twenty-five cases. J Bone Joint Surg (Am) 1973; 55: 1633-44.

6 **Jacobs PA and Clemency Jr RE.**The closed cryosurgical treatment of giant cell tumor. Clin Orthop 1985; 192: 149-58.

7 **Marcove RC, Weis LD, Vaghaiwalla MR and Pearson R.**Cryosurgery in the treatment of giant cel l tumors of bone. A report of 52 consecutive cases. Clin Orthop 1978; 134: 275-89.

8 **Marcove RC, Sheth DS, Takemoto S and Healey JH.**The treatment of aneurysmal bone cyst. Clin Orthop 1995; 311: 157-63.

9 **Marcove RC, Stovell PB, Huvos AG and Bullough PG.**The use of cryosurgery in the treatment o f low and medium grade chondrosarcoma. A preliminary report. Clin Orthop 1977; 122: 147-56.

10 **Marcove RC, Zahr KA, Huvos AG and Ogihara W.**Cryosurgery in osteogenic sarcoma: a report o f three cases. Compr Ther 1984; 10: 52-60.

11 **Vries de J, Oldhoff J and Hadders HN.**Cryosurgical treatment of sacrococcygeal chordoma. Report of four cases. Cancer 1986; 58: 2348-54.

12 **Marcove RC and Miller TR.**Treatment of primary and metastatic bone tumors by cryosurgery. JAMA 1969; 207: 1890-4.

13 **Marcove RC, Searfoss RC, Whitmore WF and Grabstald H.**Cryosurgery in the treatment of bon e metastases from renal cell carcinoma. Clin Orthop 1977; 127: 221-7.

14 **Gage AA and Torre D.** Cryosurgery. In Webster JG, ed: "Encyclopedia of medical devices an d instrumentation Vol. 2". New York, N.Y: John Wiley & Sons, 1988, 893-908.

15 **Kuflik EG and Gage AA (eds).**"Cryosurgical treatment for skin cancer", New York: Igaku-Shoin, 1990: 83-95.

16 **Gage AA, Guest K, Montes M, et al.** Effect of varying freezing and thawing rates in experimenta l cryosurgery. Cryobiology 1985; 22: 175-82.

17 **Lowdon JD and Tidmore TL Jr.**Fatal air embolism after gastrointestinal endoscopy. Anesthesiology 1988; 69: 622-23.

18 **Jacoby J, Jones JR, Ziegler J, et al.** Pneumoencephalography and air embolism; Simulate d anesthetic death. Anesthesiology 1959; 20: 336.

19 **Saha AK.** Air embolism during anaesthesia for arthrography in a child. Anaesthesia 1976; 31: 1231-3.
20 **Marcove RC.** A 17-year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1987; 163: 231-4.
21 **Schreuder HWB, van Beem HBH and Veth RPH.** Venous gas embolism during cryosurgery fo r bone tumors. J Surg Oncol 1995; 60: 196-200.
22 **Zacarian S.** Is lateral spread of freeze a valid guide to depth of freeze? J Dermatol Surg Oncol 1978; 4: 561-63.
23 **Bradley PF.** Thermography. In Bradley P (ed): "Cryosurgery of the maxillofacial region, Vol 1." Boc a Raton, Florida, CRC Press, 1986: 130-2.
24 **Ravikumar T, Kane R, Cady B et al.** Hepatic cryosurgery with intraoperative ultrasound monitorin g for metastatic colon carcinoma. Arch Surg 1987; 122: 403-9.
25 **Laugier P and Berger G.** Assessment of echography as a monitoring technique for cryosurgery . Ultrason Imaging 1993; 15: 14-24.
26 **Le Pivert P.** The measurement of low frequency electrical impedance as a guide to effectiv e cryosurgery. J Dermatol Surg Oncol 1977; 3: 395-7.
27 **Gage AA, Augustynowicz S, Montes M etal.** Tissue impedance and temperature measurements in relation to necrosis in experimental cryosurgery. Cryobiology 1985; 22: 282-8.
28 **Gage A.** Correlation of electrical impedance and temperature in tissue during freezing. Cryobiology 1979; 16: 56-62.
29 **Moser R, Abbott I, Stephens C et al.** Computerized tomographic imaging of cryosurgical icebal l formation in brain. Cryobiology 1987; 24: 368-79.
30 **Pease GR, Rubinsky B, Wong STS, et al.** An integrated probe for magnetic resonance imagin g monitored skin cryosurgery. J Biomech Eng 1995; 117: 59-63.
31 **Hong JS, Wong S, Pease G and RubinskyB.** MR imaging assisted temperature calculations during cryosurgery. Magn Reson Imaging 1994; 12:1021-31.
32 **Matsumoto R, Selig AM, Colucci VM and Jolsz FA.** MR monitoring during cryotherapy in the liver : predictability of histologic outcome. J Magn Reson Imaging 1993; 3: 770-6.
33 **Cooper I.** Cryogenic surgery for cancer. Fed Proc 1965; 24: 237-40.
34 **Bischof J, Christov K and Rubinsky B.** A morphological study of cooling rate response in norma l and neoplastic human liver tissue: cryosurgical implications. Cryobiology 1993; 30: 482-92.
35 **McGann L, Yang H and Walterson M.** Manifestations of cell damage after freezing and thawing . Cryobiology 1976; 13: 599-608.
36 **Smith JJ, Fraser J and MacIver AG.** Ultrastructure after cryosurgery of rat liver. Cryobiology 1978; 15: 426-432.
37 **Fujikawa S.** Freeze-fracture and Etching studies on membrane damage on human erythrocyte s caused by formation of intracellular ice. Cryobiology 1980; 17: 351-62.
38 **Quinn PJ.** A lipid-phase separation model of low-temperature damage to biological membranes . Cryobiology 1985; 22: 128-46.
39 **Gage A, Caruana J and Garamy G.** A comparison of instrument methods of monitoring freezin g in cryosurgery. J Dermatol Surg Oncol 1983; 9: 209-14.

CHAPTER 12

VENOUS GAS EMBOLISM DURING CRYOSURGERY FOR BONE TUMORS

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ABSTRACT

Cryosurgery using liquid nitrogen is a method for treating benign and low-grade malignant skeletal tumors. The advantage of preserving the supportive function of bone should be compared to the risk for its complications; postoperative fracture is well known, but less so the occurrence of intra-operative venous gas embolism. This paper describes 17 patients: 2 patients who had serious hemodynamic complications during cryosurgery and a study of 15 patients in whom end tidal N_2 tension was measured in an attempt to investigate the clinical incidence of venous gas embolism during cryosurgery. In the 15 cases analyzed we did not detect any exhaled N_2 during cryosurgery.

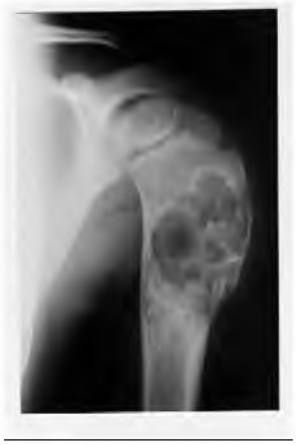
INTRODUCTION

Cryosurgery using liquid nitrogen has been practiced in orthopaedic oncology for the treatment of benign stage 2 skeletal tumors. In benign stage 3 and low-grade malignant stage IA skeletal tumors it is used in lieu of disabling wide procedures.[1,2,3] Intra-lesional resection is performed first for instance by curettage of the tumor. In theory tumor cells may be left behind, which can be responsible for a recurrence of the tumor. Adjuvant treatment is given by spraying liquid nitrogen into the lesion to extend the surgical margin of resection. By this method the procedure can be considered to be marginal from the point of view of oncologic principles.[1] The advantage of this kind of treatment, as compared to local resection, is that the supportive function of bone is preserved and that reconstructive surgery can be limited. The liquid nitrogen is sprayed into the bony cavity and since its boiling point is -195°C nitrogen bubbles are rapidly produced at room temperature. Whenever a gas is introduced into body cavity there is always the hazard of intravascular introduction of gas bubbles especially when pressure is allowed to develop. Gas emboli in the vascular circulation can cause

serious hemodynamic complications.[4,5,6] This paper demonstrates the hazards of the use of liquid nitrogen, although complications occurred in a limited amount of patients.
First, we describe two patients with hemodynamic complications during cryosurgery probably due to venous gas embolism. Because of our experiences with these two patients we conducted an additional study in 15 patients in whom end-tidal gas analysis was performed using a mass spectrometer measuring end-tidal nitrogen concentration during cryosurgery. Our aim was to get an impression of the clinical incidence of venous gas entry during cryosurgery in our institution.

CASE REPORT ONE

A 4-year-old, previously healthy boy, was suffering from an aneurysmal bone cyst proven by biopsy in his left proximal humerus (Figure 12.1). Definitive treatment was scheduled, which consisted of curettage of the cyst followed by spraying liquid nitrogen and homologous bone grafting.
Anesthesia was induced with halothane in oxygen inhalation, followed by thiopental 25 mg intravenously (iv), fentanyl 0,05 mg iv, vecuronium 2 mg iv, and 0.25 mg atropine iv. The patient was intubated and anesthesia maintained with



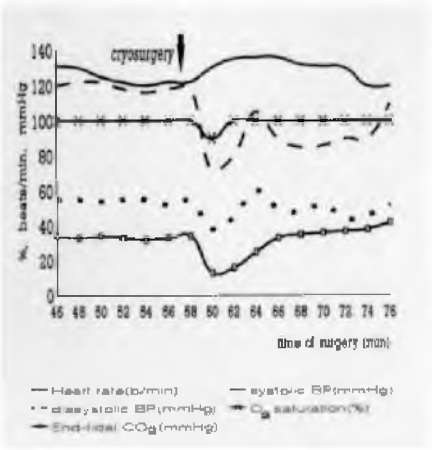


Figure 12.1 (left): An aneurysmal bone cyst in the left proximal humerus before treatment.
Figure 12.2 (right): Results of intra-operative monitoring case 1.

halothane 1-2% inspired in nitrous oxide/oxygen 70/30%. Intraoperative monitoring included electrocardiogram, pulse oximetry, automatic noninvasive blood pressure measurement and continuous end-tidal capnometry. All monitoring values were recorded automatically on an ARKIVE patient data management system on a 1-min time scale.
During the first 58 min of surgery the cyst was exposed using an anterolateral exposure and the cyst was curettaged through a surgically made cortical defect measuring 2 X 2 cm. During this time the heart rate and blood pressure ranged between 70 and 80 beats per min (bpm) and 130/60 and 114/56 respectively. End-tidal CO_2 tension was constant at 32 mm Hg. The digital pulse oximeter showed a constant 100% saturation. Vital signs and end-tidal CO_2 tension remained normal and stable up to the time of cryosurgery.
Three cycles of spraying liquid nitrogen during approximately 20 seconds and an thawing period of approximately 3 min was performed. During the last cycle, just when the nitrogen spraying was stopped a decrease of the O_2 saturation to 90% was noted. The blood pressure dropped to 70/40, together with a rise of the heart rate from 66 to 80 bpm. The end-tidal CO_2 tension decreased to 15 mm Hg. Close inspection of patient and equipment revealed no other probable cause of this event but of venous gas embolism. Nitrous oxide and halothane were stopped and 100% of O_2 was administered. Within a few minutes vital signs returned to normal and the condition of the patient stabilized (Figure 12.2). The humeral cavity was filled with a homologous bone graft and the surgical procedure was finished. The remainder of the anesthetic procedure was uneventful. The patient made a quick and complete recovery.

CASE REPORT TWO

A 26-year-old female was scheduled to undergo curettage of three chondrosarcoma grade I, stage IA lesions proven by biopsy in the right femur. One lesion was localized in the distal part of the diaphysis, one in the distal- and one in the proximal metaphysis of the right femur (Figure 12.3 and 12.4). The patient was known for bilateral retinoblastoma for which at the age of one year an excochleation of the right eye was performed and radiation therapy for the left eye. The remainder of her medical history was noncontributory. Pre-anesthetic medication consisted of midazolam 7.5 mg by mouth 1 hr before operation.
Induction of anesthesia was performed with iv midazolam 2 mg, fentanyl 0,1 mg and vecuronium 5 mg iv. Maintenance of anesthesia was achieved with a continuous infusion of propofol and artificial ventilation with a nitrous oxide / oxygen mixture 70%/30%. Intraoperative monitoring consisted of electrocardiogram, digital pulse oximeter, automatic non-invasive blood pressure measurement and continuous end-tidal capnometry. After 60 minutes of surgery the three sites had been treated by curettage and were ready for spraying liquid nitrogen. So far the vital signs had been normal and stable. During the first cycle of cryosurgery the heart rate raised from 66 to 100 beats per minute. The blood

pressure dropped to 90/40 mm Hg. The digital pulse oximeter showed a slight dip of the O_2 saturation from 100 to 98%, but the end-tidal CO_2 tension dropped to 13 mm Hg. Immediately nitrous oxide was discontinued and the patient was ventilated with 100% oxygen. The presumptive diagnosis of venous gas embolism was made. Because the vital signs did not deteriorate but improved within a few minutes, no further measures were taken (Figure 12.5). The remainder of the surgery, anesthetic and the recovery was uneventful.

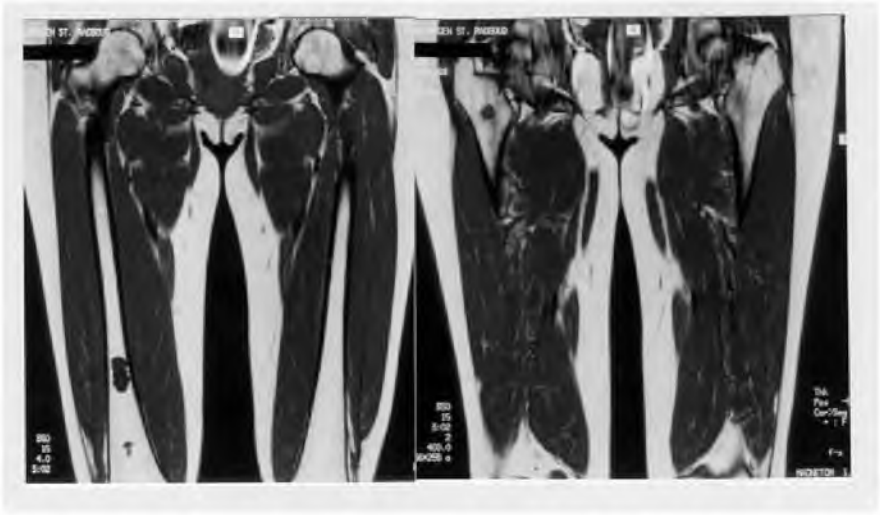


Figure 12.3 (left): MRI of the right femur showing chondroid lesions in the diaphysis and distal metaphysis of the right femur. Figure 12.4 (right): MRI of the right femur showing chondroid lesion in the proximal metaphysis.

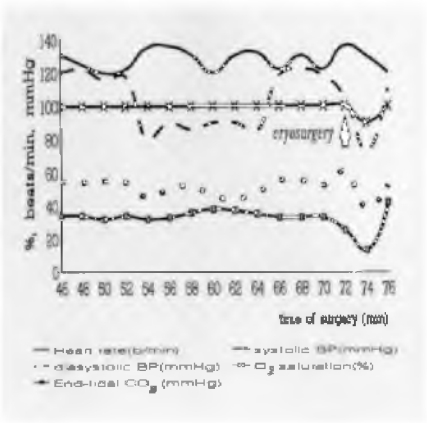


Figure 12.5: Results of intra-operative monitoring case 2.

ADDITIONAL STUDY: PATIENTS AND METHODS

We used a mass spectrometer (Ohmeda Multi gas monitor 6000) to perform end tidal gas analysis in all patients who were treated by cryosurgery. The mass spectrometer measured inhaled and end-tidal O_2, CO_2, N_2O, N_2 tensions and anesthetic vapor concentration breath by breath, starting at induction and ending just after the patient's awakening. Real-time recording of the gas analysis results was achieved by connecting a personal computer to the RS 232 port of the mass-spectrometer. Usual anesthetic monitoring equipment was used consisting of electrocardiogram, digital pulse oximeter, automatic non-invasive blood pressure measurement and continuous end-tidal capnometry. We were able to perform gas analysis in 15 patients. All patients had general anesthesia with endotracheal intubation. Their sex, age, diagnosis and site of the tumor is summarized in Table 12.1.

Case no.	Age (yr)	sex	diagnosis	site
1	12	M	benign fibrous histiocytoma	distal metaphysis femur
2	34	M	aggressive enchondroma	proximal metaphysis humerus
3	6	M	active unicameral bone cyst	proximal metaphysis humerus
4	7	M	histiocytosis X	proximal metaphysis femur
5	28	M	osteoblastoma	distal metaphysis tibiae
6	68	F	thyroid metastasis	supra-acetabular part ilium
7	47	M	lung metastasis	proximal metaphysis femur
8	24	F	giant cell tumor	distal metaphysis ulna
9	20	M	active bone cyst	os ischiadicum
10	8	M	active bone cyst	distal metaphysis femur
11	43	M	aneurysmal bone cyst	diaphysis tibiae
12	7	F	aneurysmal bone cyst	proximal metaphysis tibiae
13	36	F	chondrosarcoma	diaphysis femur
14	16	M	aneurysmal bone cyst	proximal metaphysis humerus
15	32	F	aneurysmal bone cyst	talus

Table 12.1: Clinical data of 15 patients treated with cryosurgery for bone tumors.

RESULTS

In the 15 cases analyzed, we did not detect any exhaled N_2 during cryosurgery. Also, the measured O_2, CO_2, N_2O tensions and anesthetic vapour concentration were completely normal. All patients had an uneventful course.

DISCUSSION

In the literature, one fatal case, probably due to venous gas embolism, has been described. The occurrence was explained by the blocking of the exit of gaseous nitrogen from the bone by intentional digital occlusion of the opening in the bone cortex.[7]

Dwyer et al. reported one case in which a dramatically increased end-tidal nitrogen tension was noted, but without any hemodynamic complications.[8] These investigators estimated that the use of only 38 ml of liquid nitrogen will rapidly vaporize into approximately 27.4 L of N_2 gas. So small amounts of liquid nitrogen can be responsible for a large volume (embolus) of intravascular gas.

Two dogs died because of cardiac arrest after liquid nitrogen was instilled into the mandibular marrow cavity. Resuscitation was unsuccessful and postmortem radiographs of the thorax showed air in the veins of the mediastinum, right atrium and ventricle.[9]

Our two patients showed signs of impairment of pulmonary circulation as indicated by a sudden significant drop in end tidal CO_2 and corresponding changes in blood pressure and heart rate. We suggest that these features represent venous gas embolism because of their rapid development at the same time as the instillation of the liquid nitrogen and the fact that the symptoms disappeared rather quickly after the cryosurgery was ended. Solid particle embolism by marrow or fat is less likely, because this kind of embolism is provoked by mechanical elevation of the intramedullary pressure as in intramedullary nailing and introduction of a prosthesis.[10,11]

We think that N_2 bubbles are "pushed" into the venous circulation under influence of the pressure due to boiling of liquid nitrogen in the bony cavity. Dissolving N_2 in blood first is highly unlikely because of its very low Oswald solubility coefficient (C=0,015 at 37°C).

We are unable to estimate the amount of liquid N_2 we are using in our cases. We are spraying and not pouring the liquid N_2 into the bony cavity for as long we think is necessary to produce the required zone of subzero temperature. Based on the observations we made in two out of 17 patients, it seems that there may be a much higher risk of nitrogen gas embolism during cryosurgery, than might be gained from the only two reports in the literature. The risk is increased when the site of the tumor is located in a richly perfused area such as the metaphysis of the long bones where the major nutrient arterial and venous blood supply is entering the medullar cavity. Unfortunately, the metaphysis is the location of preference for many bony tumors suitable for cryosurgical treatment.

Using cryosurgery one should never block the entrance to the bony cavity. Appropriate diagnostic monitoring (end-tidal CO2 or preferably N_2 tension) should be in use. Nitrous oxide should be avoided as it potentially could increase the size of N2 bubbles. It might be wise to investigate the use of liquid oxygen or carbon dioxide which by its high solubility in blood is much less likely to produce pulmonary embolism.

REFERENCES

1 **Enneking WF.** A staging system of staging musculoskeletal neoplasms. Clin Orthop 1986; 204: 9-24.

2 **Malawer MM and Dunham W.** Cryosurgery and acrylic cementation as surgical adjuncts in th e treatment of aggressive (benign) bone tumors. Clin Orthop 1991; 262: 42-57.

3 **Eckardt JJ and Grogan TJ.** Giant cell tumor of bone. Clin Orthop 1986; 204: 45-59.

4 **Lowdon JD and Tidmore TL Jr.** Fatal air embolism after gastrointestinal endoscopy. Anesthesiology 1988; 69: 622-23.

5 **Jacoby J, Jones JR, Ziegler J, et al.** Pneumoencephalography and air embolism; Simulate d anesthetic death. Anesthesiology 1959; 20: 336.

6 **Saha AK.** Air embolism during anaesthesia for arthrography in a child. Anaesthesia 1976; 31: 1231-3.

7 **Marcove RC.** A 17- Year review of cryosurgery in the treatment of bone tumors. Clin Orthop 1982; 163: 231-4.

8 **Dwyer DM, Thorne AC, Healey JH and Bedford RF.** Liquid nitrogen instillation can cause venou s gas embolism. Anesthesiology 1990; 73: 179-181.

9 **Harvey HJ.** Fatal air embolization associated with cryosurgery in two dogs. J Am Vet Med Assoc 1987; 173: 175-6.

10 **Pell ACH, Christie J, Keating JF and Sutherland GR.** The detection of fat embolism b y transoe sophageal echocadiography during reamed intramedullary nailing: a study of 24 patients wit h femoral and tibial fractures. J Bone Joint Surg (Br) 1993; 75-B: 921-5.

11 **Christie J, Burnett R, Potts HR and Pell ACH.** Echocardiography of transatrial embolism durin g cemented and uncemented hemiarthroplasty of the hip. J Bone Joint Surg (Br) 1994; 76-B: 409-12.

CHAPTER 13

SUMMARY AND CLOSING REMARKS

Active and aggressive benign and low-grade malignant skeletal tumors are commonly treated by intralesional curettage. Additional adjuvant treatment to extend the surgical margin is used to destroy tumor cells left behind, which otherwise may be responsible for a recurrence of the tumor.
This thesis describes the use of a specific type of locoregional adjuvant therapy: *cryosurgery*. It is the destruction of tissue in situ through the local influence of very low temperatures.
The following is a summary of this thesis. For discussion of the presented topics the reader is referred to the specific chapters. Finally, this paragraph is finished with closing remarks.

In **chapter 1** the aims of the thesis are posed; description of effective cryosurgery, review of the literature, evaluation of clinical results of cryosurgery for bone tumors and the development of equipment and results of local and general monitoring of cryosurgery are shown.

In **chapter 2**, it becomes clear that the therapeutic use of low temperatures has a long historical background and that it has found its way in almost every medical specialty.
Its anaesthetizing properties were first recognized. Later its benefits for the palliative treatment of malignancies was much appreciated. At that time the potential properties of very low temperatures for destroying tissue were recognized.
The development of suitable machinery for the application of very low temperatures to induce a cold injury to a specific target area of tissue, now known as *cryotherapy* or *cryosurgery*, gave the physicians a powerful tool in their armour for the treatment of benign and malignant tumors.

Using cryosurgery in modern medicine in general and for bone tumors in particular, it is necessary to investigate and formulate all basic factors and principles to perform a "state of the art" cryosurgical treatment.
The basic principles for effective cryosurgery for bone tumors are formulated in **chapter 3.** Different kind of cryoprobes are compared and it is concluded that an open cryoprobe producing a liquid nitrogen spray has an extremely high cooling power (-175°C). It is the most suitable probe to freeze the irregular surface of bony cavities left behind after the curettage of bone tumors and is capable to achieve very rapid freezing rates.
Monitoring the cryosurgical process is of importance to ensure an effective treatment and to avoid an unwarranted extension of the freeze causing potential morbidity. Several monitoring devices are described and it is concluded that the

local positioning of thermocouples mounted in the tip of a needle is the only practical solution for the monitoring of cryosurgery for the treatment of bone tumors.

Cryobiology; the study of physical effects of low temperatures on living tissue is described in **chapter 4**. It explains the lethal properties of a cold injury to an individual cell. It also directs the most effective method of cryosurgery; very rapid cooling which induces intracellular ice formation causing lethal mechanical damage to cell membranes, temperatures as low as -50°C and slow thawing creating intracellular *re*crystallization of water and again membrane damage. Repetitive cycles of freezing and thawing is furthermore a prerequisite and is a practical solution to treat areas of insufficient freezing during previous cycles and to compensate for the capability of living tissue to resist a thermal injury.

A literature review, with the intention to be complete, is presented in **chapter 5**. Using MEDLINE EXPRESS 1965 - 1996 all experimental and clinical data on cryosurgery with specific reference to the skeletal system are summarized. From this review it is concluded that frozen bone is devitalized within one week. Osteogenesis originating from normal bone and periosteum adjacent to the frozen segment is observed within several days. Revitalization of the dead bone by simultaneous resorption and reossification will take several months.
Studies on the efficacy of adjuvant therapies in terms of inducing additional peripheral necrosis after curettage showed that cryosurgery is superior as compared to phenolization and cementation.
The clinical use of cryosurgery on specific benign bone tumors, described in series of 25 patients or more, is very limited and conducted in less than 5 different institutions. In terms of tumor control the results are good to excellent although the complication rates are high but diminish to acceptable figures according to the non-preventable learning curve. All other applications of cryosurgery, especially in medium and high grade malignant lesions of bone are confined to case reports or very small series of patients (less than 10), experimental and above all, palliative with regard to tumor control.

Chapter 6 describes the largest series ever published of patients with simple bone cysts treated by curettage, cryosurgery and bone grafting. Forty-two patients were retrospectively studied of which 38% had failed prior treatment; injections with steroids and or curettage with or without bone grafting. After a mean clinical follow-up of 24.5 months five patients (12%) had a local recurrence. Compared to historical controls gathered from the literature this recurrence rate is much better than curettage and bone grafting which has a recurrence rate of 29%. Injection with steroids is associated with a recurrence rate of 11%. These data are very much influenced by the inventer of this particular therapy and were never confirmed by others in comparable size of series of patients and its recurrence rate is therefore likely to be more significant.

In 1995 Marcove, the "father of cryosurgery for bone tumors" published a series of 51 aneurysmal bone cysts all treated with curettage, cryosurgery and bone grafting and reported a recurrence rate of 17.6%. This rate was an improvement as compared to historical controls treated with curettage and bone grafting with a recurrence rate of 30.8%. In **chapter 7** a multicenter study of 27 aneurysmal bone cysts is presented all treated with curettage, cryosurgery and bone grafting. A recurrence rate of 4% was observed after a mean follow-up of 47 months. It is concluded that this kind of treatment gives comparable local tumor control as marginal (en block) resection, but without the need for more extensive reconstructive surgery with associated morbidity. The study presented is a conformation of Marcove's results with respect to the treatment of aneurysmal bone cysts by cryosurgery.

Eosinophilic granuloma is preferably treated by local injection of steroids, but some fail to respond or are unsuitable for this kind of therapy due to location, (pending) pathological fracture and/or soft tissue involvement. In **chapter 8** the use of cryosurgery for six of these type of eosinophilic granuloma of bone are described. After a mean follow-up of 23.3 months all lesions healed with one complication (pathological fracture).

In **chapter 9** a case report of a patient, known for bilateral retinoblastoma, with three chondroid lesions in the intramedullary space of one femur is presented. All lesions were treated with curettage, cryosurgery and bone grafting. After 33 months of follow-up, there are no signs of recurrence. This case is *the* example of an efficient treatment with a minimal loss of bone stock, making reconstruction of bony defects easy as compared to segmental, marginal resections.

The clinical, radiographical and histological diagnosis and treatment of intramedullary chondroid lesions in the extremities is one of the controversies in orthopaedic oncology. In **chapter 10** a specific approach consisting of radiographic work-up (plain X-ray, bone scan, MRI or CT), biopsy and definite treatment is presented. The technique of cryosurgery is described in detail. Twenty-two patients with 26 lesions were studied and after a mean follow-up of 25 months no recurrences were observed and all patients had excellent functional results.

For the local monitoring of the cryosurgical process during repetitive freeze and thaw cycles a computerized temperature measuring system with peroperative real-time graphic visualization was developed and the clinical application is presented in **chapter 11**. An in vivo study of 15 cryosurgical procedures showed that using a liquid nitrogen spray intralesional temperatures of -150°C were achieved within 10 seconds after the freeze was started.
Continuous spraying for 15 to 20 s resulted in an intralesional temperature of -50°C or below during a mean of 39.3 s. Spontaneous thawing between -50° and 0°C took on the average 152.6 s. In this period the increasing temperature

frequently entered a subzero plateaux phase varying in time from 20 to 250 s. Thawing from zero to 20°C required in general 290 s. In general the whole area around the frozen lesion cools down making the time needed for thawing to 20°C after every freeze longer. Reviewing the monitoring data it is concluded that this system is of value to ensure that the cryosurgical procedure is sufficient, but perhaps more important, is perfectly capable preventing unwarranted local extent with unnecessary morbidity. Furthermore, it is shown cryosurgery carried out with a spray is a reproducible method.

In **chapter 12** the issue of venous gas embolism during cryosurgery for bone tumors is investigated. Because of the experience with two patients who had serious cardio-pulmonary disfunction during the freezing of their bone lesions which were in all probability the result of venous gas embolism, a study of 15 patients was conducted in which end tidal N_2 tension was measured in an attempt to investigate the incidence of gas embolism during cryosurgery. Although in these patients no exhaled N_2 was detected, it is concluded that venous gas embolism during cryosurgery using a spray is a significant complication and that the avoidance of building high pressure in the cavity is of paramount importance.

In general the following orthopaedic bone tumors are suitable for the cryosurgical technique described in this thesis:

* unicameral (simple) bone cyst
* aneurysmal bone cyst
* giant cell tumor
* eosinophilic granuloma
* intramedullary chondroid lesions:
  - enchondroma
  - chondrosarcoma grade 1
  - chondroblastoma
  - chondromyxoid fibroma
* fibrous dysplasia
* intramedullary hemangioma
* intramedullary schwannoma

In specific circumstances the technique can be of value for the treatment of malignant lesions of bone. These are:

* marginal resection of the tumor is, due to its location, not possible or induces unacceptable morbidity like in vertebral (chordoma) and pelvic lesions.
* marginal or wide resection is not indicated, but beneficial for local control of the tumor like metastasis of bone.

Cryosurgery for bone tumors is most effectively executed with an open probe producing a liquid nitrogen spray. Local and general monitoring is advocated for a sufficient treatment and for safety of the patient. An autologous or homologous bone graft will eventually incorporate and will restore the normal architecture of the bone. During this remodeling process the extremity is weakened and partial weightbearing is indicated for at least 10 weeks postoperative. Diaphyseal lesions of the femur and tibiae should be protected against fracture with prophylactic internal fixation using plate and screws.

CONCLUSIONS AND ADDRESS OF THE AIMS OF THIS THESIS

1 This thesis defines the theoretical, technical and practical requisites for the effective execution of a "state of the art" cryosurgical treatment as adjuvant to intralesional resection of benign and low-grade malignant bone tumors.

2 This thesis contains a literature review which provides experimental evidence that cryosurgery is more capable to induce bone necrosis than phenol and cement. Furthermore, it shows that cryosurgery has been effectively used as adjuvant treatment for benign and low-grade malignant bone tumors.

3 This thesis describes a total of 101 of such bone tumors in 96 patients, in 6 of which a local recurrence occurred; a rate of 5.9%.
Five wounds (5.0%) became infected, two (2.0%) operations were complicated by a transient nerve palsy and 6 (6.3%) by postoperative pathological fracture. All patients had an excellent functional outcome.

4 This thesis reports on the development and results of a local monitoring system of the cryosurgical process in vivo. The system is of value to perform an effective freeze and to avoid an unwarranted extent of the cold injury to surrounding tissue.

5 This thesis describes the incidence and magnitude of venous gas embolism during cryosurgery for bone tumors recorded with general monitoring.
It is a continuing source for major concern and extreme caution during cryosurgery.

PROBLEMS AND QUESTIONS REMAINING

Although the clinical results of cryosurgery are very promising and from the view of tumor control are at least equal and in the opinion of the author of this thesis better than other means of adjuvant treatment, there are some clinical problems remaining. This thesis describes several monitoring devices to prevent complications. Local monitoring using thermocouples has been shown to be very helpful in preventing unwarranted freezing of important structures adjacent to the lesion. But the exact extent and thus adjuvant therapy in terms of surgical margin is not known, other than the intralesional surface temperature. The process of cryosurgery, especially the duration of the freeze, is still much dependable on clinical judgement.

With close systemic monitoring it is possible to detect venous gas embolism during cryosurgery. As shown in this thesis this is a serious complication and so far only one death has been reported. Measuring end tidal N_2 reveals venous gas embolism late, possibly to late, *after* there initiating.
Endo-oesophageal ultrasound of the heart will detect venous gas embolism a stage earlier, but again after the damage has already been done. Although we have limited experience with its use, endo-oesophageal ultrasound is at this moment the best technique. However, we do not know what precise echo images we have to look for; big "solid" or more "foamy, snowstorm" patterns?
The mechanism of N_2 embolism is unclear. Gas bubbles or liquid nitrogen directly pushed into the venous circulation is one of the possibilities.
When during cryosurgery the surface of the cavity is getting extremely cold, the additional sprayed liquid nitrogen will not be able to vaporize. In stead, the bone marrow gets the properties comparable to a sponge and sucks the liquid nitrogen in small marrow spaces. This liquid nitrogen may get trapped in these marrow spaces. When thawing or a rise of the temperature is allowed, the trapped liquid nitrogen will boil and vaporize building extremely high pressures.
It may be possible that under these circumstances liquid nitrogen or gaseous nitrogen is pushed into the venous circulation*.
It may be possible that we have to look for venous gas embolism in more centrally located veins like in the abdomen or thorax.

Postoperative fracture of the remodelling bone subjected to cryosurgery, is not only very distressing for the patient, but also compromises the orthopaedic oncologic status; first there was an *intra*-compartimental disease, due to the fracture it has now potentially changed to an *extra*-compartimental disease.
In our experience fracture is most likely to occur one to four weeks after the cryosurgical treatment. We do not know the biological course concerning strength of bone after cryosurgery.

** personal communication with J. van Egmond*

The bony defects resulting after curettage of bone tumors are generally filled with a bone graft. For tumor control it is probably useless as has been shown in the results of the treatment of unicameral and aneurysmal bone cysts. Furthermore it is a potential cause of transmitting diseases and infection.
Is the use of a bone graft to reconstruct the bony defect helpful in healing this defect? Does it strengthen the bone, does it accelerate the restoration of the bony architecture? If so, what source is best, allograft or autograft?
Research investigating these questions is currently directed in this way in an effort to answer these questions.

SAMENVATTING EN AFSLUITENDE OPMERKINGEN

Actieve en agressieve goedaardige en laaggradig kwaadaardige bottumoren worden in het algemeen behandeld met intralesionale resectie. Aanvullende therapie met het doel de chirurgische marge te vergroten wordt gegeven om achtergebleven tumor cellen te vernietigen, welke anders verantwoordelijk kunnen zijn voor een recidief van de tumor.
Dit proefschrift beschrijft het gebruik van een specifiek type aanvullende behandeling: *cryochirurgie.* Het is de destructie van weefsel in situ door de lokale inwerking van zeer lage temperaturen.
Het onderstaande is een een samenvatting van het proefschrift. Voor een uitgebreide discussie van de verschillende onderwerpen wordt de lezer dezes verwezen naar de specifieke hoofdstukken, hoewel aan het einde van deze paragraaf enkele afsluitende opmerkingen worden gemaakt.

In **hoofdstuk 1** worden de doelstellingen van het proefschrift geformuleerd; de beschrijving van effectieve cryochirurgie, een overzicht van de literatuur, een evaluatie van de klinische resultaten van cryochirurgie van bottumoren en de ontwikkeling van instrumenten en resultaten voor lokale en systemische bewaking alsmede monitoring tijdens cryochirurgie.

In **hoofdstuk 2** wordt het duidelijk dat het therapeutisch gebruik van lage temperaturen een lange historische achtergrond heeft en haar toepassing heeft gevonden in bijna elk medisch specialisme. De verdovende eigenschappen van lage temperaturen werden het eerst onderkend. Later werden de voordelen als verzachtende behandeling van kwaadaardige tumoren erg gewaardeerd. In die tijd werd de potentiële kracht voor weefseldestructie door lage temperaturen herkend.
De ontwikkeling van geschikte apparaten voor het induceren van een koude letsel in een specifiek doelgebied, nu bekend onder de naam *cryochirurgie* of *cryotherapie*, gaf de medici een krachtig wapen in handen voor de bestrijding van goedaardige en kwaadaardige tumoren.

Als men, in tijden van moderne geneeskunst gebruik wil maken van cryochirurgie in het algemeen en voor bottumoren in het bijzonder, is het noodzakelijk om alle basale factoren en principes te onderzoeken en te formuleren, zodat een "state of the art" cryochirurgische behandeling kan worden uitgevoerd.
De basale principes, die ten grondslag liggen aan een effectieve cryochirurgie van bottumoren, worden geformuleerd in **hoofdstuk 3**. Verschillende typen cryoprobes worden vergeleken en geconcludeerd wordt dat een open cryoprobe, die een spray van vloeibare stikstof produceert, een extreme hoge koeling capaciteit heeft (-175°C). Deze is het meest geschikt voor het bevriezen van irregulaire oppervlakten van benige holten, zoals die achterblijven na de curettage van bottumoren. Daarnaast is het met open cryoprobes mogelijk om zeer hoge bevriezingssnelheden te bereiken.

Het monitoren van het cryochirurgische proces is van belang om een effectieve behandeling te garanderen en om een ongewilde uitbreiding van het vriesletsel te voorkomen, welke een potentiële bron voor morbiditeit zou kunnen zijn. Verschillende monitorings mogelijkheden worden beschreven en geconcludeerd wordt dat het lokale gebruik van temperatuursensoren, gemonteerd in het uiteinde van een holle naald de meest praktische oplossing is voor het monitoren en bewaken van cryochirurgie voor de behandeling van bottumoren.

Cryobiologie; de studie van fysieke effecten van lage temperaturen op levend weefsel wordt beschreven in **hoofdstuk 4**. Cryobiologie verklaart de destruerende eigenschappen van een koude letsel aan een individuele cel. Het geeft ook aan hoe de meest effectieve wijze van cryochirurgie dient te worden uitgevoerd; zeer snelle bevriezing, die gepaard gaat met een dodelijke intracellulaire ijsvorming door mechanische beschadiging van de celmembranen, een minimum temperatuur van -50°C en langzame ontdooiing. Dit laatste gaat opnieuw gepaard met intracellulaire rekristallisatie van water en dus opnieuw met membraan beschadiging. Verder is het herhalen van vries en dooi cycli vereist en een praktische oplossing voor de behandeling van insufficiënt bevroren gebieden tijdens eerdere cycli en voor het compenseren van de capaciteit van levend weefsel om een thermische beschadiging te weerstaan.

Een literatuur overzicht, met de intentie compleet te zijn, wordt gepresenteerd in **hoofdstuk 5**. Door gebruik te maken van MEDLINE EXPRESS 1965 - 1996 worden alle experimentele en klinische data betreffende cryochirurgie in relatie tot het skelet samengevat. Uit deze gegevens wordt het duidelijk dat bevroren bot binnen een week avitaal is. Osteogenesis voortkomend uit normaal bot en botvlies vlak naast het bevroren bot begint binnen enige dagen. Revitalisatie van dood bot door gelijktijdige resorptie en verbening duurt enige maanden.
Experimenten betreffende de effectiviteit van aanvullende behandeling voor het verkrijgen van perifere additionele necrose na curettage, laten zien dat cryochirurgie superieur is aan het gebruik van fenol en cement.
Het klinisch gebruik van cryochirurgie beschreven in series van 25 of meer patiënten met specifieke bottumoren is schaars en uitgevoerd in minder dan vijf verschillende instituten in de wereld. Wat betreft de controle van de tumoren zijn de resultaten goed tot uitstekend. Aanvankelijk werden hoge aantallen complicaties gerapporteerd, maar deze dalen, conform de niet te vermijden leercurve tot een acceptabel niveau.
Toepassingen van cryochirurgie voor de behandeling van middel en hooggradige tumoren van bot zijn niet alleen beperkt gebleven tot publikaties van aparte ziektegeschiedenissen (minder dan 10), maar ook experimenteel en wellicht palliatief in de zin van tumorcontrole.

Hoofdstuk 6 beschrijft de grootste serie ooit gepubliceerd betreffende patiënten met simpele botcysten behandeld met curettage, cryochirurgie en botgrafting.
Retrospectief werden 42 patiënten bestudeerd; 38% had een eerdere gefaalde

behandeling ondergaan met injectie van steroiden en/of curettage met of zonder botgrafting. Na een gemiddelde follow-up van 24,5 maanden hadden vijf patiënten (12%) een lokaal recidief. Vergeleken met het percentage van 29% bij controle patiënten behandeld met curettage en botgrafting verzameld in de literatuur is dit beter. Injectie therapie met steroiden heeft een recidief percentage van 11%. Dit percentage wordt erg beïnvloed door de uitvinder van deze therapie en werd nooit herhaald door anderen in vergelijkbare series van patiënten. Het recidief percentage is daarom waarschijnlijk hoger.

In 1995 publiceerde Marcove, die het gebruik van cryochirurgie voor bottumoren introduceerde, een serie van 51 patiënten met een aneurysmatische botcyste, allen behandeld met curettage, cryochirurgie en botgrafting en rapporteerde een recidief percentage van 17,6%. Dit percentage is een verbetering vergeleken met een historische controle groep van patiënten behandeld met curettage en botgrafting, die een recidief percentage van 30,8% kent. In **hoofdstuk 7** wordt een studie beschreven van 27 aneurysmatische bot cysten, alle behandeld in de academische ziekenhuizen van Nijmegen en Groningen met curettage, cryochirurgie en botgrafting. Na een gemiddelde follow-up van 47 maanden werd een recidief percentage van 4% geconstateerd. Geconcludeerd wordt dat deze behandeling vergelijkbare lokale controle van de tumor geeft als marginale resectie, maar zonder de noodzaak voor een soms ingewikkelde benige reconstructie, wat met een hogere kans op additionele morbiditeit gepaard gaat.
De gepresenteerde studie is de eerste die de resultaten van Marcove voor dit type tumor bevestigd.

Eosinofiele granulomen van bot worden bij voorkeur behandeld met de intralesionale injectie van corticosteroiden. Helaas reageren sommige eosinofiele granulomen van bot niet op deze behandeling of zijn ongeschikt om op dergelijke wijze te behandelen. Dit kan komen door een ongunstige lokatie, een dreigende pathologische fractuur en/of weke delen uitbreiding. In **hoofdstuk 8** worden 6 van dergelijke eosinofiele granulomen van bot besproken, alle behandeld met cryochirurgie. Na een gemiddelde follow-up van 23,3 maanden zijn alle lesies genezen. Er was één complicatie in de zin van een pathologische fractuur, welke na osteosynthese restloos is genezen.

In **hoofdstuk 9** wordt een patiënt beschreven die in één femur twee enchondromen en een chondrosarcoom graad 1 ontwikkelde 25 jaar nadat zij behandeld werd voor een retinoblastoom van beide ogen. De drie chondroide tumoren werden behandeld met curettage, cryochirurgie en botgrafting. Na een follow-up van 33 maanden zijn er geen tekenen van een recidief. Deze ziektegeschiedenis is hèt voorbeeld van de botsparende eigenschappen van deze behandeling, zonder toe te geven aan de effectiviteit in de zin van controle van de tumor.

Over de klinische, radiologische en histologische diagnose en behandeling van intramedullaire kraakbenige tumoren in de ledematen, bestaat enige onenigheid binnen de groep van specialisten die zich bezig houdt met orthopaedische oncologie. In **hoofdstuk 10** wordt een specifieke benadering bestaande uit radiologisch onderzoek (röntgenfoto's, CT of MRI), biopsie en definitieve behandeling middels curettage en cryochirurgie gepresenteerd. De techniek van cryochirurgie wordt tot in detail besproken.
22 Patiënten met 26 lesies werden aldus behandeld en na een gemiddelde follow-up van 25 maanden werden geen lokale recidieven waargenomen en alle patiënten hadden een excellent functioneel resultaat.

De ontwikkeling van een temperatuur meetsysteem voor de lokale monitoring van vries/dooi cycli wordt in **hoofdstuk 11** gepresenteerd. Het systeem maakt gebruik van temperatuursensoren, waarvan de gemeten temperaturen grafisch op een computer monitor (real-time) kunnen worden afgelezen. Een in vivo studie van 15 cryochirurgische procedures liet zien, dat bij gebruik van een vloeibare stikstof spray, intralesionale temperaturen van -150°C kunnen worden bereikt. Wordt het sprayen gedurende 15 tot 20 seconden voortgezet dan blijft de intralesionale oppervlakte temperatuur gedurende 40 seconden onder -50°C.
Spontane ontdooiing tussen de -50°C en 0°C nam ongeveer 152 seconden in beslag. In deze periode werd vaak een net onder de 0°C gelegen plateau fase gezien, waarin de temperatuur niet lineair met tijd steeg. Verder opwarmen van het bevroren weefsel van 0 tot 20°C duurde gemiddeld ongeveer 290 sec.
In het algemeen koelde het gehele gebied af wat de opwarmtijd van de tweede en derde cyclus steeds langer maakte.
Op grond van deze data kan men concluderen dat dit meetsysteem bijdraagt aan het verhogen van de effectiviteit van cryochirurgie en waardevol is bij het voorkomen van een te groot koude letsel resulterend in onnodige morbiditeit.
Ook werd duidelijk dat het gebruik van een spray een goed reproduceerbare methode voor het uitvoeren van cryochirurgie is.

In **hoofdstuk 12** wordt het fenomeen en een studie van veneuze gas embolieën tijdens cryochirurgie besproken. Dit naar aanleiding van twee patiënten bij wie, tijdens een cryochirurgische behandeling, ernstige cardio-pulmonaire complicaties optraden, waarschijnlijk als gevolg van dergelijk embolieën.
Bij 15 patiënten werd tijdens cryochirurgie de stikstofspanning in de uitademingslucht gemeten met behulp van een massaspectrograaf in een poging een idee van de incidentie van veneuze stikstofembolieën te verkrijgen. Ondanks dat bij geen enkele patiënt N_2 in de uitademingslucht werd geconstateerd, kan cryochirurgie gepaard gaan met cardio-pulmonaire instabiliteit, die waarschijnlijk het gevolg is van veneuze stikstof embolieën. Derhalve dient tijdens cryochirurgie met een spray het opbouwen van druk in de intramedullaire ruimte te worden voorkomen.

In het algemeen zijn de volgende botumoren geschikt voor de cryochirurgische techniek zoals beschreven in dit proefschrift:

* unicamerale (simpele) botcyste
* aneurysmatische botcyste
* reusceltumor
* eosinofiel granuloom
* intramedullaire chondroïde lesies:
  - enchondroma
  - chondrosarcoma graad 1
  - chondroblastoom
  - chondromyxoid fibroom
* fibreuze dysplasie
* intramedullair haemangioom
* intramedullair schwannoom

In geval van specifieke omstandigheden kan deze techniek ook van waarde zijn bij de behandeling van kwaadaardige bottumoren. Deze zijn:

* marginale resectie van de tumor is niet mogelijk of zou resulteren in onaanvaardbare morbiditeit. Deze situatie doet zich met name voor bij tumoren gelocaliseerd in de wervelkolom (chordoom) en bekken.
* marginale of ruime resectie is niet geïndiceerd, maar locale controle is gewenst. Deze situatie doet zich soms voor bij de behandeling van ossale metastasen.

Cryochirurgie van bottumoren wordt het meest efficient uitgevoerd met een open probe, die een vloeibare stikstof spray produceert. Locaal en algemeen monitoren en bewaken is noodzakelijk voor een sufficiënte behandeling en veiligheid van de patiënt.
Een autologe of homolge botgraft zal uiteindelijk incorporeren en de normale architectuur van het bot herstellen. Gedurende dit remodellerings proces is het bot minder sterk en is in geval van de onderste extremiteit voor minstens 10 weken slechts partieel belastbaar. Diafysaire femorale en tibiale lesies dienen profylactisch met interne fixatie te worden verstevigd.

CONCLUSIES EN BESCHOUWING VAN DE DOELSTELLINGEN VAN DIT PROEFSCHRIFT

1 Dit proefschrift definieert de theoretische, technische en praktische voorwaarden voor de uitvoering van een "state of the art" cryochirurgische behandeling als aanvulling op intralesionale resectie van goedaardige en laaggradig kwaadaardige bottumoren.

2 Dit proefschrift bevat een overzicht van de literatuur, waaruit blijkt dat er sterke aanwijzingen zijn dat cryochirurgie beter in staat is tot het veroorzaken van necrose van bot dan phenol and cement.
Uit het overzicht blijkt verder dat cryochirurgie met succes als adjuvans is gebruikt voor de behandeling van goedaardige en laaggradig maligne bottumoren.

3 Dit proefschrift beschrijft 101 van dergelijk bottumoren bij 96 patiënten, alle behandeld met curettage en cryochirurgie. Zes lesies (5,9%) recidiveerden lokaal. Bij vijf patiënten (5.0%) raakte de wond postoperatief geïnfecteerd, twee (2,0%) operaties werden gecompliceerd door een voorbijgaande uitval van een zenuw. Hoewel er zes (5,9%) pathologische fracturen optraden, hadden alle patiënten uiteindelijk een excellent functioneel resultaat.

4 Dit proefschrift beschrijft de ontwikkeling van een lokaal monitoring en bewakings systeem van cryochirurgie in vivo. Het systeem draagt bij aan een effectieve cryochirurgische behandeling en aan het voorkomen van een onbedoelde uitbreiding van het koude letsel in het omgevende weefsel.

5 Dit proefschrift beschrijft de incidentie en ernst van veneuze gasembolieën in patiënten. Het is een blijvende zorg en vereist een continue alertheid.

RESTERENDE PROBLEMEN EN VRAGEN

Hoewel de klinische resultaten van cryochirurgie veelbelovend zijn en wat betreft de lokale controle van de tumor op zijn minst gelijk zijn, en naar de mening van de schrijver van dit proefschrift zelfs beter dan andere vormen van adjuvante behandeling, resteren er een aantal klinische problemen. Dit proefschrift beschrijft een aantal bewakings en monitor mogelijkheden voor het vermijden van complicaties. Lokale monitoring met behulp van temperatuurmetingen is zeer geschikt voor de preventie van een te uitgebreide vrieslesie, die anders omgevende belangrijke structuren zou beschadigen. De precieze uitbreiding van dit vriesletsel blijft echter onduidelijk en dus ook de mate van de aanvullende weefsel necrose. Het gehele cryochirurgische proces, met name de duur van het vriezen blijft voor een belangrijk deel afhankelijk van de klinische blik.

Met algemene anaesthesiologische bewaking van een patiënt is het mogelijk veneuze gasembolieën te signaleren, hetgeen een levensbedreigende complicatie kan zijn. Het meten van N_2 in de uitademingsgassen detecteert gasembolieën laat, mogelijk te laat, *na* het ontstaan van veneuze gasembolieën.
Met endo-oesophageale echografie van het hart kunnen gasembolieën een stadium eerder worden waargenomen, maar nog steeds nadat het kwaad al is opgetreden. Hoewel we slechts minimale ervaring hebben met deze techniek, lijkt deze momenteel het beste. Helaas weten we niet precies wat voor echobeelden afwijkend zijn en hoe deze er uitzien; zijn het grote solide emboliën of meer kleine "schuimachtige, sneeuwstorm" patronen?
Het mechanisme van ontstaan van gasembolieën is ook onduidelijk. Worden gasbelletjes of vloeibare stikstof direct in de veneuze circulatie geperst?
Als de oppervlakte van een benige holte tijdens cryochirurgie extreem koud wordt dan krijgt deze de fysische eigenschappen van een spons. Vloeibare stikstof wordt in het beenmerg gezogen en het is voorstelbaar dat het daar in de kleine trabeculaire structuren "gevangen" raakt. Bij opwarmen zal opgesloten vloeibare stikstof verdampen wat gepaard gaat met de opbouw van zeer hoge drukken. Het is mogelijk dat onder deze omstandigheden stikstofgas of vloeibare stikstof in de circulatie wordt geperst*.
Het is misschien noodzakelijk om in meer centraal gelegen veneuze vaten te kijken zoals bijvoorbeeld in het abdomen.

Postoperatieve fracturen zijn niet allen voor de patiënt erg vervelend, maar compromitteren ook de oncologische situatie; was er eerst sprake van een *intra*-compartimentele ziekte, dan is deze door de fractuur veranderd in een potentiële *extra*-compartimentele ziekte.
Onze ervaring is dat pathologische fracturen het vaakst enkele weken na de cryochirurgische behandeling optreden. Helaas ontbreekt ons het inzicht in het biologische verloop van de sterkte van bot na cryochirurgie en hoe dit

* *Persoonlijke communicatie met J. van Egmond*

gerelateerd is aan het remodellerings proces.
De botdefecten die overblijven na curettage en cryochirurgie worden doorgaans gevuld met een botgraft. Voor de additionele waarde in de zin van tumorcontrole heeft het geen zin, zoals gedemonstreerd in de resultaten van de behandeling van unicamerale en aneurysmatische botcysten. Botdonaties blijven, ondanks de zorgvuldige testen, een bron van overdraagbare ziekten en infectie.
Is het gebruik van een botgraft dan nuttig voor het helen van het defect? Helpt het het bot te versterken en wordt het herstel van de botstructuur versneld? Zo ja, wat is beter; een allograft of autograft?
Onze huidige onderzoeken worden momenteel in deze richting geredigeerd.

DANKWOORD

In het derde jaar van mijn opleiding tot orthopaedisch chirurg maakte ik op indringende wijze kennis met de orthopaedische oncologie door het werk van Prof.Dr. R.P.H. Veth. Mijn interesse werd door hem herkend en aangemoedigd. "Begeestering" mijnerzijds volgde.
Cryochirurgie stond wekelijks op het programma; een bijna magische behandeling met disco-achtige stikstof dampen in de operatiekamer. Een onderzoeks project was snel gevonden en heeft geresulteerd in dit proefschrift.
Om mijn wens te specialiseren in de orthopaedische oncologie werd, met de steun van velen, maar van met name Prof. Veth, een KWF fellow-ship voor de duur van twee jaar door mij verworven. René, heel hartelijk dank voor..... alles.

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Heel veel liefs en dank daarvoor.

CURRICULUM VITAE

Hendrik Willem Bartho Schreuder werd op 1 juni 1961 in Schiedam geboren.
De middelbare school werd met een Atheneum B diploma afgesloten en in 1979 werd aangevangen met studie geneeskunde aan de medische faculteit van de Erasmus Universiteit te Rotterdam. Het artsexamen werd in januari 1987 behaald.

In 1987 en 1988 vervulde hij zijn dienstplicht als luitenant ter zee, arts bij de Koninklijke Marine.

De vooropleiding heelkunde werd volbracht in het Ikazia Ziekenhuis te Rotterdam onder leiding van Dr. A.P. Brinkhorst gedurende de jaren 1989 en 1990.

De opleiding orthopaedie werd januari 1991 gestart in het Academische Ziekenhuis te Nijmegen, aanvankelijk onder leiding van Prof.Dr. T.J.J.H. Slooff en later Prof.Dr. R.P.H. Veth. Op 1 januari 1995 vond registratie als orthopaedisch chirurg plaats.

Gedurende de jaren 1995 en 1996 werd een KWF fellow-ship "orthopaedische oncologie" volbracht (begeleider: Prof.Dr. R.P.H. Veth). Gedurende dit fellow-ship vond uitzending gedurende een half jaar plaats naar de Sarcoma Service van het Academisch Ziekenhuis van de University of Washington, Seattle, USA (begeleider: E.U. Conrad III, MD). In het kader van het fellow-ship werden werkbezoeken gebracht aan Prof.Dr. A.H.M. Taminiau in het Academisch Ziekenhuis te Leiden en Prof.Dr. J.W. van der Eyken in het Onze Lieve Vrouwe Gasthuis en Academisch Ziekenhuis te Amsterdam.

Sinds 1 januari 1997 is de schrijver dezes werkzaam op de afdeling orthopaedie van het Academische Ziekenhuis te Nijmegen.