CRYOSURGERY OF BONE TUMORS

COMPLICATIONS, ANIMAL EXPERIMENTS, AND CLINICAL RESULTS

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Medische Wetenschappen

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For Wieteke, Jens, Marijn, Lies and Josien
to my parents

Chapter 1

GENERAL INTRODUCTION AND AIMS OF THE STUDY

GENERAL INTRODUCTION

Destroying diseased tissue like benign and malignant neoplasms during a surgical procedure is known as cryosurgery. In the treatment of benign and low-grade malignant bone tumors, curettage of the tumor with subsequent local adjuvant cryosurgery will result in the destruction of remaining tumor cells and extension of the surgical margin. From an oncological point of view, cryosurgery makes an intralesional treatment of bone tumors equivalent to a marginal excision[2,10]. Benign bone tumors are frequently located in the vicinity of joints and functional growth plates. Marginal excision of the tumor will jeopardize these structures and may result in a poor functional outcome. The main advantage of cryosurgical treatment of bone tumors is the preservation of bone stock and joints, which makes reconstructive procedures of segmental bone defects and joints unnecessary. Marcove, a pioneer in the field of cryosurgery of bone tumors, reported his first promising results in 1968[8]. Cryosurgery appeared to be a powerful and flexible tool, capable of creating a necrotic margin of more than 1 cm in bone[7]. Despite Marcove's success in reducing the local recurrence rate, cryosurgery did not become generally accepted in the treatment of bone tumors. Reasons for this were the high complication rate and the unpredictability of the depth of the freeze that gave cryosurgery a poor reputation. However, well-respected surgeons in the field of Orthopedic Oncology, who had strong reservations to cryosurgery of bone tumors, did never prove their arguments with data[3,4].

Since its introduction, cryosurgical technique has been strongly improved. Efforts have been made to dose the liquid nitrogen, applied to the bony lesion by an open (direct pouring/spraying) or closed (metal cryoprobe) system. By means of local temperature registration, an unwarranted freeze of adjacent tissues, with potential destructive effects, can be controlled[1,9].

After cryosurgery of the lining of a bony lesion, cells will die but the matrix persists[6]. It is assumed that revitalization of necrotic bone is accompanied by further weakening of local bone stock, already compromised by tumor[5]. This phenomenon explains the frequently encountered pathological fractures after cryosurgical treatment. In this respect, further improvement of the treatment is advisable.

AIMS OF THE STUDY

Aims of the study are:

1. To qualify, quantify and discuss the complications related to cryosurgical treatment of bone tumors.
2. To study the local temperature field and thermodynamics in bone tissue during cryosurgery, and to relate the temperature field to the extent of necrosis.
3. To examine the reduction of bone strength after cryosurgical treatment of long bones in time. To study the correlation between the mechanical characteristics of cryosurgically treated bone and its remodeling process.
4. To study the influence of bone grafting on the healing of cryosurgically treated gap defects in long bones.
5. To report on further results of cryosurgically treated patients with fibrous dysplasia and giant cell tumor of bone.

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Chapter 2

CRYOBIOLOGY AND IT'S EXPLOITATION TO INDUCE CELL DEATH

H.W.Bart Schreuder, Lucien C.M. Keijser and René P.H. Veth

Book chapter: Cryosurgery in the treatment of bone tumors. Malawer (ed.). Churchill Livingstone, New York. In press.

Cryobiology is the study of the physical effects of low temperatures and in practice the changing of temperatures in living tissues. 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 of the main component of tissues; 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 the 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[1]. Crystallization requires initiating nuclei, for instance an insoluble crystalline impurity[44]. 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 re-crystallization to minimize their surface energies[9].
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 re-crystallization of the thermodynamically unstable small crystals. The temperature at which both solute and solvent will become solidified is called the eutectic temperature.

TEMPERATURE CHANGES IN TISSUE

Cryosurgery consists of four basic features; freezing, holding of the freeze, thawing and repetition of freeze/thaw cycles. The nature of the tissue response varies with the intensity. A minor cryogenic injury produces only an inflammatory response, a greater injury will produce tissue destruction. The effects of every physical state on living tissue can be divided in immediate and in delayed effects. Immediate destructive properties of cryosurgery are the result of freezing and thawing, whereas the delayed effects are due to progressive failure of the microcirculation (vascular stasis), tissue ischemia and ultimately cell death[19]. When tissue temperature is lowered without reaching subzero temperatures, cell metabolism falls. This is a reversible process, and used to its benefit in cardiac surgery. However, if living tissue is continuously subjected to low, but non-freezing temperatures, cell death will occur.
In the next paragraphs the destructive effects of changing temperatures on living tissue will be discussed.

CRYOSURGICAL FACTORS INDUCING CELL DEATH

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 contains substances with high and low molecular weight, which lower the freezing temperature. 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[6].
Factor 1 for cryosurgical induced cell death: the shrinkage and high concentration of solutes, especially of salts, may be responsible for cell injury[19,29]. This phenomena seems especially of importance during slow cooling rates.

Very rapid cooling induces intracellular ice formation, because there is insufficient time for water leaving the cell to maintain osmotic equilibrium across the cell membrane[5]. 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[40], and disturbs the function of mitochondria[10] and other cell organelles and membranes[11,33,36,41]. The injury to cells occurring during rapid cooling is called *thermal shock*.
Factor 2 for cryosurgical induced cell death: intracellular ice formation induces disruption of cell organelles and membranes.

Masses of frozen cells, closely packed will be subjected to shearing forces of ice formation which will injure the tissue structure. Propagating ice formation will induce cell damage, regardless of the fact that ice is intra- or extracellular[19]. Intracellular ice has been shown to propagate from one cell to another via intercellular channels[3].
Factor 3 for cryosurgical induced cell death: mechanically induced tissue and cell destruction due to propagation of ice formation.

During thawing the "behavior" of the ice crystals is dependent on the rate of thawing. In contrast to rapid thawing, slow thawing is accompanied by re-crystallization and the crystals can grow to damaging sizes[2,19]. The damaging effect of these intracellular ice crystals, only formed during rapid freezing can therefore be exploited a second time, if slow thawing is allowed, thereby enhancing re-crystallization. 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[34].
Factor 4 for cryosurgical induced cell death: large ice crystals, due to re-crystallization during thawing, disrupt cells and cell organelles.

After thawing there is typically a brief period of vasodilatation. 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[37,38].
The importance of post-thaw 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[7]. Histological examination of these

tumors revealed widespread vascular thrombosis. In bone, microangiography has demonstrated a total avascularity of the cortex to cryosurgery[24].
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.
Factor 5 for cryosurgical induced cell death: tissue ischemia due to microcirculatory failure.

PRACTICAL CONSIDERATIONS FOR EFFECTIVE CRYOSURGERY

Cooling rate
As noted above rapid cooling rates in the order of 50°C/min will definitely induce the formation of intracellular ice crystals. Irrespectively of the cryosurgical technique used, these kind of cooling rates are only achieved close to the source of the freeze, whereas at the periphery of the freeze much lower cooling rates are encountered. Fortunately, experiments have shown that intracellular ice formation does also appear at lower cooling rates, but seems to be more dependent on the kind of tissue frozen. For instance in slices of liver, intracellular ice was noted at a cooling rate of 22°C/min[5] and in neoplastic cells frozen in vitro at only 3°C/min[23]. Therefor, the cooling rate perse is not the primary factor for cell death, but that cells are subjected to diverse thermal profiles for different times[19].

Temperature
How low should the temperature be, in order to be lethal? The answer to this question depends upon where the temperature is measured: close to the 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[28], it was soon turned into less than -20°C[8,22]. Authors of later experiments on animals advocated temperatures between –20° to -30°C[45]. In some in vitro experiments total cell death was achieved only with temperatures of –40° to -50°C[38]. In treating cancer cells, the minimum in vivo temperature advised is -50°C[14,27,32,35]. In 1979 -30°C was thought to produce a marginally lethal injury. Therefor, a safer technique was proposed especially for neoplastic tissue. It required 40°C in normal tissue surrounding the lesion[16]. Gage et al advocated the -60°C isotherm beyond the periphery of the lesion as adequate treatment[17].
So with all these different experiments it is difficult to establish the lethal temperature. The kind of cell is of importance and it seems that neoplastic cells need an absolute lower temperature than normal cells, as shown recently in adenocarcinoma cells in rats, which needed a lethal temperature of -70°C[42].

Duration of freezing
Experiments have shown that cell destruction is increased in rapidly frozen tissue that was held frozen for a period, when compared to a cryosurgical cycle without holding of the freeze[15,18,42]. In tissue with a temperature in range of -40°C and above the phenomena of solute effects and re-crystallization occur with its additional destructive properties. Below -40°C all tissue is solidly frozen and holding the freeze at these temperatures seems therefore of less importance[19].

Thawing rate
The most important part of a cryosurgical cycle is thawing. During thawing, especially in the range from -40°C and above the phenomena of solute effects and re-crystallization occur as was noted before. The longer the thawing, the larger the icecrystals will grow, the more the mechanical damage to the cells will be. Therefor, thawing should be allowed spontaneously and complete.

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 because it is technically demanding to achieve optimal conditions for cell death in all areas of the lesion. To compensate, repetition of freeze/thaw cycles is a practical solution that 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[4,15,20,35].
Mallon and Dawber performed a clinical study, in which one and two freeze/thaw cycles were compared in the treatment of basal cell carcinoma. A 95% cure rate was achieved with a cryosurgical treatment utilizing two cycles, as compared to 79% with only one cycle[30].

In summary, cryosurgery is most effective in inducing cell death and tissue necrosis when the following features are employed: rapid cooling, temperatures as low as -50°C, when technically possible holding of the freeze between of -40°C and above, slow spontaneous thawing and repetitive freeze/thaw cycles.

CRY0BIOLOGY WITH SPECIFIC REFERENCE TO BONE

Extensive research has been done to establish the histological changes of bone after it has been subjected to low temperatures.
Gage and Emmings 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[13]. The animals were subsequently sacrificed at various time 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 such as 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 non-vital 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 with resorption of bone was apparent. Fractures of the femurs were common during this time. Long term observation indicated that the whole process of resorption and revitalization ending up in complete repair took about one year[13].

These histological sequences were acknowledged by Hausamen who froze the mandibles of rabbits, and by Schargus et al who froze rabbit tibias[21,39]. 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 radiological 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 remodeling 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[12].
Marcove 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[31].
Kuylenstierna et al 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[25]. These results further supported the hypothesis that post-cryosurgical 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[24].
Kuylenstierna et al proved in further experiments, using fluorochrome labeling, that early (4 weeks) revitalization of the medullary cavity occurred in concurrence with his angiographic results, thus demonstrating the importance of intramedullary (endosteal) osteogenesis[26].

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Chapter 3

COMPLICATIONS OF CRYOSURGERY

H.W.Bart Schreuder, Lucien C.M. Keijser and René P.H. Veth.

Book chapter: Cryosurgery in the treatment of bone tumors. Malawer (ed.). Churchill Livingstone, New York. In press.

Every surgical treatment, and especially a relatively new surgical treatment will be accompanied by complications. Cryosurgery is no exception in this respect. In general, complications will diminish not only along the learning curve of the physicians starting the new treatment, but also due to improvement of the technique itself. Recording the quality and quantity of complications is the first step in the process of avoiding them! Afterwards, research is of importance to optimize the efficacy of the treatment with an (never) acceptable complication rate. In this chapter, complications of cryosurgery for bone tumors and some guidelines to avoid them are described.

WOUND INFECTIONS

Intralesional excision (curettage) of an intramedullary tumor will leave behind a cavity with a lot of dead space. Cryosurgery results in a supplementary amount of tissue necrosis. Furthermore, most surgeons are filling this defect with a "dead" homologous bone graft and sometimes an osteosynthesis is added. All these factors are strong mediators for developing a bacterial infection. In Table 3-I, data from the literature addressing infection related to cryosurgery are summarized.

Table 3-I
Data of studies addressing postoperative wound infections after adjuvant cryosurgery of bony lesions

Author	No. of patients	No. of infections	Comments
Schreuder[31]	42	2 (5%)	superficial infections
Malawer[14]	25	-	
Malawer[15]	102	-	
Marcove[18]	18	-	
Marcove[19]	52	8 (15%)	
Marcove[21]	7	2 (29%)	all sacral lesions
Marcove[22]	51	-	
Total	297	12 (4%)	

As in all other surgical procedures in which foreign bodies are implanted, postoperative wound infections are of major concern. Procedures in which cryosurgery is utilized are no exception in this respect. The question is whether the use of cryosurgery itself is responsible or the cause of infections and whether cryosurgical procedures per se are associated with a higher infection rate compared to other similar procedures? Similar procedures in Orthopedic Oncology with the same goal are the use of phenol or cement with or without bone grafting and osteosynthesis. Literature data on this subject are rare, but do report low infection rates[3,28].
Cryosurgery seems to be accompanied with an infection rate of about 4%, but this differs between institutions. Definition and reports of infections, for instance deep or superficial infections and prolonged wound drainage, are not always clear or comparable in the literature listed in Table 3-I. Sacral lesions are prone for developing an infection.

In general, infection rates decline along the learning curve (Figure 3-1). To avoid infections after a cryosurgical procedure the following items are of importance:

1. The use of peri-operative, broad spectrum antibiotics.
2. Adequate drainage of wound fluids. It is our clinical observation that there is some kind of reactive hyperemia in the area of cryosurgery just after the freezing is stopped. This may lead to a large wound hemathoma and the risk of infection.
3. Adequate wound exposure with retraction and protection of the skin with gauzes is necessary to avoid accidental freezing of the skin.
4. Wound closure with sufficient soft tissue coverage.

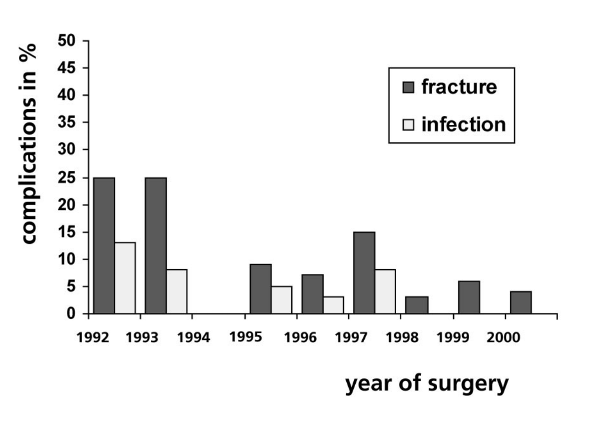

Figure 3-1. Prospectively registered percentage of postoperative pathological fractures and deep wound infections after cryosurgical treatment of 220 bone tumors at the University Medical Centre Nijmegen (UMCN), in the period 1992-2000. Notice the decreasing incidence of deep wound infections since cryosurgery was introduced at the UMCN in 1992, illustrating the effect of the learning curve of a physician starting a new treatment. Because of frequently encountered postoperative pathological fractures, preventive titanium plate fixation was gradually introduced for diaphyseal lesions. The number of pathological fractures observed declined.

VENOUS GAS EMBOLISM

Illustrative case report

An aneurysmal bone cyst in the left humerus of a four-year-old boy was treated with curettage, adjuvant cryosurgery, and homologous bone grafting (Figure 3-2). Anesthesia was induced with halothane in oxygen inhalation, followed by thiopental 25 mg i.v., fentanyl 0.05 mg i.v., vecuronium 2 mg i.v., and 0.25 mg atropine i.v.. The patient was intubated and anesthesia maintained with halothane (1%-2%) inspired in nitrous oxide/oxygen (70%/30%). During the first 58 min of surgery, the cyst was exposed and curettaged through a cortical window, measuring 2 X 2 cm. During this time, the heart rate and blood pressure ranged between 70-80 beats per min (BPM) and 130/60-114/56 mm Hg, respectively. End-tidal CO_2 tension was constant at 32 mm Hg. The digital pulse oximeter showed a stable 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 a thawing period of approximately 3 min were performed. During the last cycle, just when the liquid nitrogen spraying was stopped, a decrease of the O_2 saturation to 90% was noted. The blood pressure dropped to 70/40 mm Hg, the heart rate increased from 66 BPM to 80 BPM, and the end-tidal CO_2 tension decreased to 15 mm Hg (Figure 3-3). 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

Figure 3-2. Pre-operative anteroposterior radiograph of an aneurysmal bone cyst in the left humerus of a four-year-old boy.

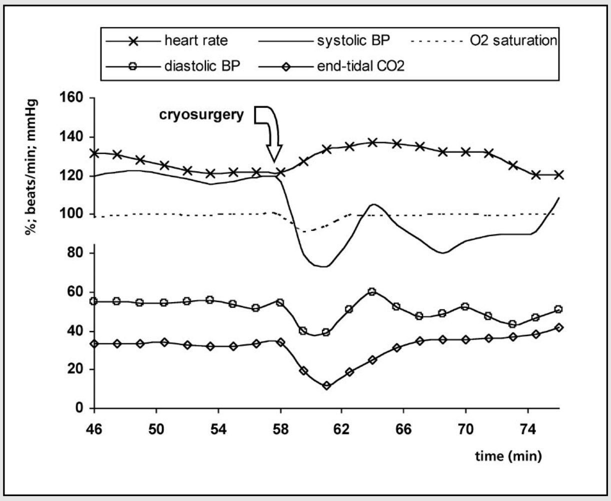

Figure 3-3. Results of intra-operative systemic monitoring, showing the event of venous gas embolism during cryosurgery.

administered. Within a few minutes, vital signs returned to normal and the condition of the patient stabilized. 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.

During cryosurgery, liquid nitrogen is either sprayed or poured into the bony cavity. Since its boiling point is -195°C, nitrogen gas-bubbles are rapidly produced at room temperature. In general, whenever a gas is introduced into a body cavity there is 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[10,12,26].

Dwyer et al. reported a presumed incident of venous gas embolism during a cryosurgical procedure in which a dramatically increased end-tidal nitrogen tension was noted, but without any hemodynamic complications[5]. 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.

In the literature, one fatal case due to venous gas embolism during cryosurgery has been described. This case 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[20].

We reported two patients, who showed signs of impaired pulmonary circulation during cryosurgical procedures, as indicated by a sudden drop in end tidal CO_2 and corresponding changes in blood pressure and heart rate[30]. We suggested that these features represent venous

gas embolism, because of their rapid development at the same time as the instillation of the liquid nitrogen, and because of the fact that the symptoms disappeared quickly after the cryosurgery had come to an end[30]. 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[4,24]. De Vries conducted experiments in rats and rabbits to evaluate the problem of bone marrow embolism during cryosurgery[34]. It was concluded that the intravasation of bone marrow was caused by increased intramedullary pressures. Embolization of bone marrow was encountered, but not on a large scale. Most of the bone marrow intravasations remained locally in the extraosseous veins[34].
In the veterinarian literature two dogs are described, which died because of cardiac arrest after liquid nitrogen was poured 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[8]. This report confirms our observation during obduction of a goat which died in a cryosurgical experiment; the venous system was filled with a kind of "bloody foam", representing numerous small gasembolisms. In a clinical experiment, we used a mass spectrometer (Ohmeda Multi gas monitor 6000) to perform end tidal gas analysis in patients whom were treated by cryosurgery[30]. 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. In 15 consecutive cases analyzed, we did not detect any exhaled N_2 during cryosurgery. Also, the measured O_2, CO_2, N_2O tensions and anesthetic vapor concentration were completely normal. All patients had an uneventful course. Furthermore, in five patients we performed endo-oesophageal ultrasound cardiography in an attempt to detect venous gas embolism prior to its passage to the lungs. We did not see any abnormal ultrasound pictures in concordance with gasembolism.

The mechanism of N_2 embolism is unclear. 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 may absorb the liquid nitrogen in its small marrow spaces. When thawing or a rise of the temperature is allowed, the trapped liquid nitrogen will boil and vaporize, building up high pressures. It may be possible that under these circumstances liquid nitrogen or gaseous nitrogen is forced into the venous circulation. Dissolving N_2 in blood at first is highly unlikely, because of its low Oswald solubility coefficient at body temperature (C=0.015).
The risk is increased when the site of the tumor is located in cancellous bone, such as the metaphysis of the long bones. 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. 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.

FRACTURES

The tumor itself, as well as the surgical exposure and resection jeopardize the structural integrity of the bone. Cryosurgery is said to further diminish bone strength with time, often leading to postoperative fractures.
In the late sixties, the pioneers of cryosurgery in the field of bone tumors reported high fracture rates. In Table 3-II, a summary is given of published series of 15 or more cases of bone tumors treated with adjuvant cryosurgery.

Table 3-II
Reported series of more than 15 cases on adjuvant cryosurgery of bone tumors. Data are listed with reference to diagnosis and postoperative pathological fractures

Author	Type of tumor	No. of patients	No. of fractures
Marcove[17]	giant-cell tumor	25	8 (32%)
Marcove[18]	chondrosarcoma grade 1 and 2	18	6 (33%)
Marcove[19]	giant-cell tumor	27	5 (19%)
Marcove[22]	aneurysmal bone cyst	51	5 (10%)
Russe[25]	various benign bone tumors	26	1 (4%)
Malawer[14]	various benign bone tumors	25	2 (8%)
Malawer[15]	giant cell tumor	102	6 (6%)
Schreuder[31]	simple bone cyst	42	2 (5%)
Total		316	35 (11%)

Research on animals has given insight in the process of healing of cryosurgically treated bone. This revitalization process is held responsible for loss of bone strength. Gage and Emmings 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[7]. The animals were subsequently sacrificed at various time intervals and the bones excised. 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 consisting of osteogenesis initiated by vital bone and periosteum at the border of the devitalized segment. After 1 month a thin layer of subperiosteal new bone covered the nonvital shaft. In time, this layer thickened and at approximately 4 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 1 and 2 months, revascularization and resorption of bone were apparent. Fractures of the femur were common during this time. Necrotic cortical bone was slowly replaced by vital bone. Long term observation indicated that the whole process of resorption and revitalization ending in complete repair took about 1 year.
The effect of cryosurgery on the strength of bone was tested by Fisher et al[6]. The mandibles of rats had a reduction in strength of approximately 40%, 8 weeks after cryosurgery. The gradual loss of strength in these bones paralleled observed radiographic osteolysis. At 4 months, the mandibles had regained strength accompanied by clear radiographic evidence of sclerosis. Although not

investigated in this experiment, the gradual loss and return of strength in cryosurgically treated bone is thought to parallel histological evidence of bone resorption, repair and remodeling[7,27]. McCord and Bradley investigated the effect of two ceramic materials, dense hydroxyapatite and beta tricalcium phosphate, implanted over cryosurgically treated mandibles of rats at a subperiosteal level[23]. Not only were the results of Fisher et al confirmed, but both materials were found to prevent the loss of strength due to cryosurgery by hyperplasia of the subperiosteal immature bone.

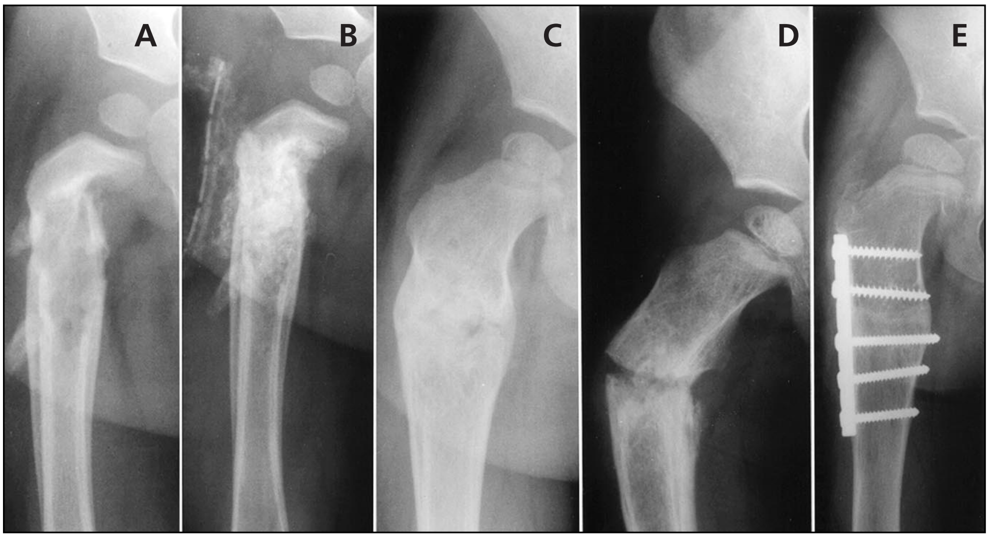

Figure 3-4. Pre-operative anteroposterior radiograph of the right femur of a two-year-old girl with an osteolytic lesion due to eosinophilic granuloma of bone (A). Radiographs after curettage, adjuvant cryosurgery and homologous bone grafting (B), and at 5 months follow-up (C). Pathological fracture 8 months after the operation (D); local recurrence was ruled out by histological examination. Consolidation 5 months after internal fixation (E).

Postoperative fracture of the remodeling bone subjected to cryosurgery is not only very distressing for the patient, but also compromises the orthopedic oncologic status. The fracture may potentially change an intra-compartimental disease into an extra-compartimental disease. In our experience, fractures are most likely to occur 4 to 8 weeks after the cryosurgical treatment, but they can occur even 8 months after cryosurgery (Figure 3-4). Diaphyseal lesions are prone for pathological fractures, and prophylactic internal fixation should be considered (Figure 3-5). We use a titanium plate and screws, which protects the bone especially for rotating forces. An intramedullary enforcement is ill advised, because it has the risk of contaminating the entire intramedullary compartment with tumor cells. Titanium alloys have our preference, because these implants induce little interference on MRI, making tumor follow-up less difficult. Partial weightbearing is usually necessary until three months after the operation.
Experience and improvements in technique have reduced the fracture rate to an acceptable level (Figure 3-1). Since we use prophylactic osteosynthesis, sometimes in combination with cement and or bone graft, we do not observe fractures anymore (Figure 36). This is in concurrence with the experience of Malawer et al[15].

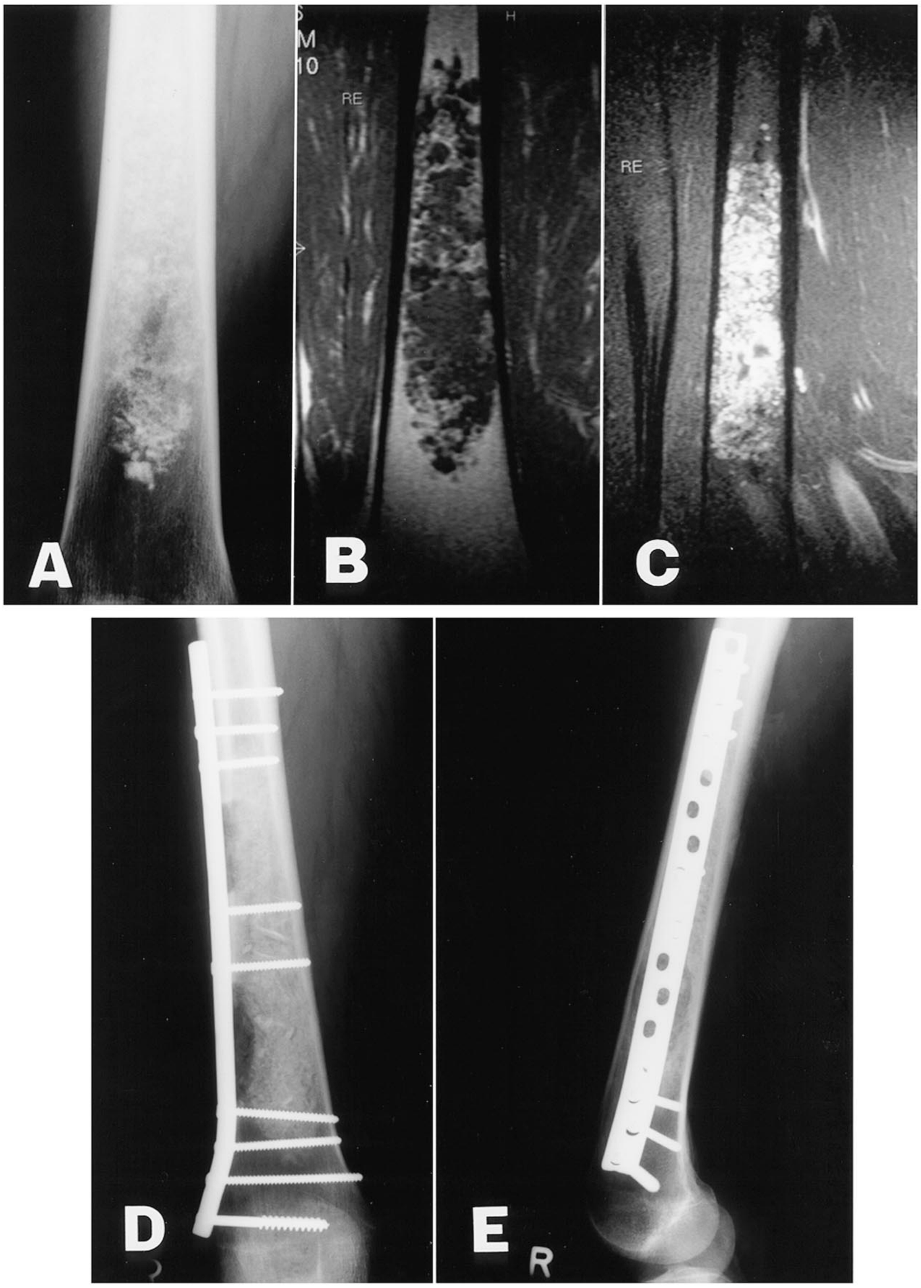

Figure 3-5. Routine anteroposterior radiograph of a 65-year-old man with a chondrosarcoma grade 1 of the right femur (A). T1 weighted magnetic resonance imaging (MRI): coronal view before (B) and sagital view after (C) administration of gadolinium. Routine radiographs 4 months after curettage, adjuvant cryosurgery, osteosynthesis and homologous bone grafting through two separate cortical windows (D,E).

Figure 3-6. Routine radiographs of a pathological intra-articular fracture of the left distal femur in a young woman due to a giant cell tumor (A,B). Postoperative radiographs after intralesional excision, reduction with some intentional shortening, adjuvant cryosurgery, homologous bone grafting, and cementation of the lateral femoral condyl with titanium alloy osteosynthesis to achieve stability (C,D). Consolidation 37 months post treatment without signs of local recurrence (E,F).

DAMAGE TO THE EPIPHYSIS

Benign bone tumors, especially simple bone cysts and aneurysmal bone cysts tend to occur in patients with an immature skeleton. These tumors are commonly developing in the metaphysis, often adjacent to the epiphysis. Damage of the epiphysis either by the tumor itself or by the use of cryosurgery is very well possible and may result in arrest or disturbance of normal growth.
Lenz et al and Schneider 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[11,29].
Malawer and Dunham reviewed 25 pediatric patients with aggressive benign tumors, all treated by cryosurgery[14]. They saw two patients with damage to the epiphysis necessitating surgical epiphyseal arrest of the contralateral side. During surgery, no attempt was made to prevent the epiphysis from freezing, control of tumor was their first priority.
Schreuder et al reported on 42 treated simple bone cysts of which 11 were located in the proximal metaphysis adjacent or close to the epiphysis[31]. During surgery, care was taken not to damage the adjacent physis by curettage and if the physis was exposed to the cyst, it was excluded from freezing by several layers of surgical gelfoam. No growth disturbances were seen, but two local recurrences were encountered[31].
Our experience indicates that freezing the epiphysis will result in damage even as the result of not very low temperatures, as is illustrated in Figure 3-7.

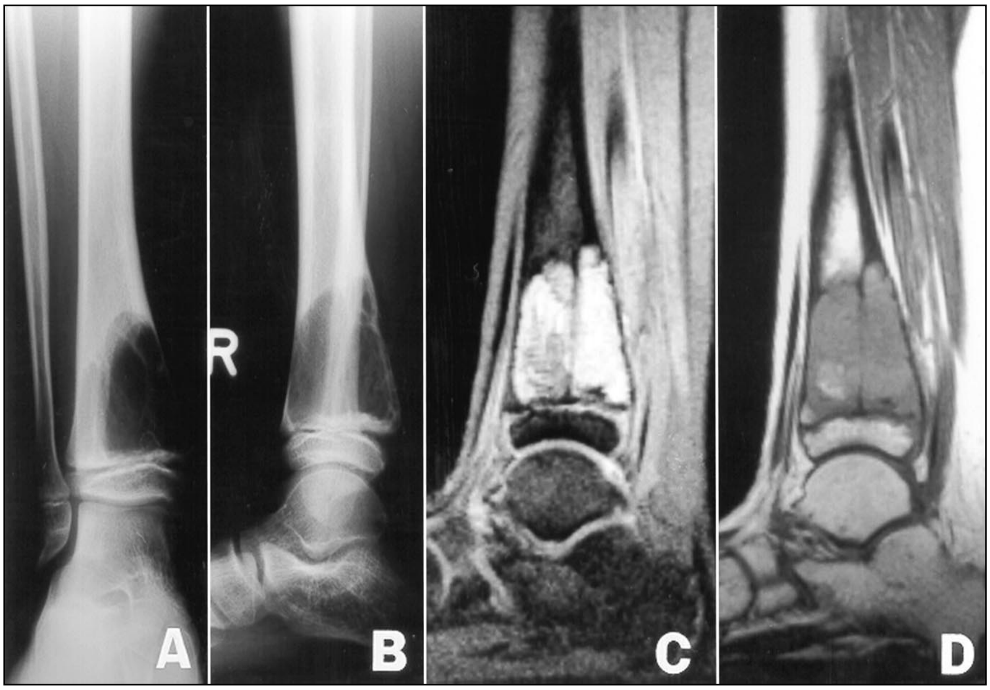

Figure 3-7-1.1. Routine radiographs of an eleven-year-old boy with an aneurysmal bone cyst in the distal tibia, extending close to the growthplate (A,B). T2 weighted (C) and T1 weighted (D) magnetic resonance imaging, showing erosion of the cortex and a fairly homogenous intensity of the lesion consistent with fluid. The cyst seems not to have damaged the epiphysis.

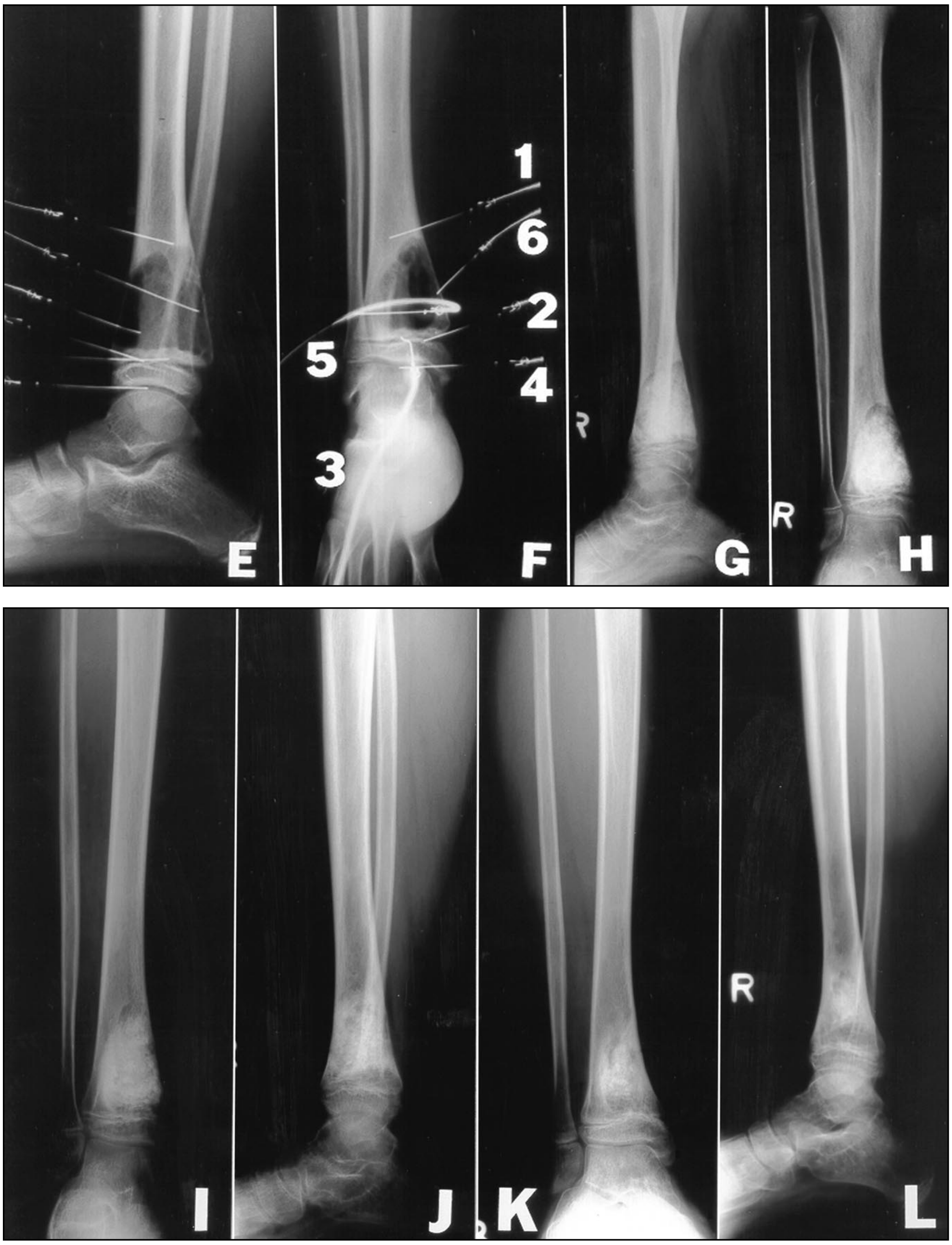

Figure 3-7-1.2. Intra-operative radiographs (E,F) showing needle-mounted thermocouples located in the growthplate (no. 2 and 3) and the joint space (no. 4). The intralesional located needle no. 7 was added later. Needle numbers correspond with those in Figure 3-7-2. After curettage and adjuvant cryosurgery the cyst is filled with a homologous bone graft (G,H). Routine radiographs at 9 (I,J) and 16 (K,L) months post treatment: suspicion of gradually closing of the medial part of the distal epiphysis, but no evident varus bowing. Closure of the medial part of epiphysis 40 months post treatment with resulting varus deformity (M,N,O).

Figure 3-7-1.3. Closure of the medial part of epiphysis 40 months post treatment with resulting varus deformity (M,N,O).

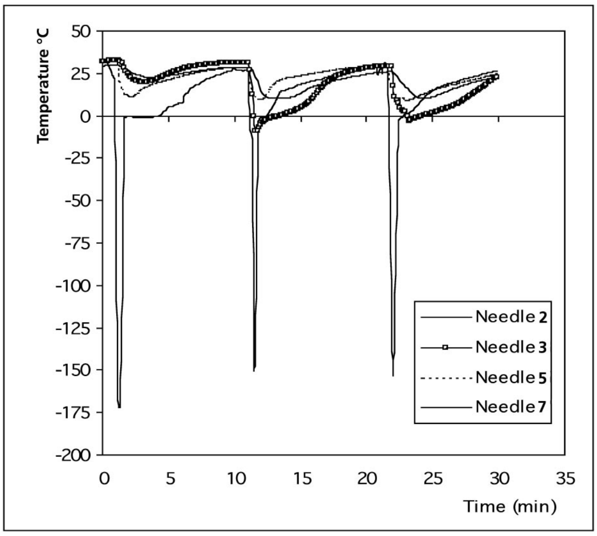

Figure 3-7-2. Intra-operative temperature recordings of the patient in Fig. 3-7-1 (E,F): the recording of number 3, next to number 2 of the epiphysis, shows subzero temperatures during the second and third freeze cycle, evidently just enough to damage the epiphysis resulting in a local growth arrest. The temperature measured by the thermocouples 1, 4 and 6 were at all times above 25°C. For reasons of clarity of the graph they are not shown.

Whether an epiphysis is damaged by the bone tumor or by the treatment will not always become clear and in many cases may be the result of both. Protection of an exposed epiphysis by gelfoam to minimize the risk for damage seems feasible. On the other hand, gelfoam lowers the effectiveness of the cryosurgery with the increasing risk of local tumor recurrence, which may potentially damage the epiphysis after all. Monitoring freeze/thaw cycles with thermocouples may be beneficial in controlling a cryosurgical procedure and may prevent an unwarranted local extent of the freeze. This counts especially for lesions close to, but not "in touch" with the epiphysis.

DEGENERATIVE OSTEOARTHRITIS

Some bone tumors like giant cell tumor and chondroblastoma are almost always located close to major joints. Damage of the articular surface, either by the tumor itself (intra-articular fracture) or by the treatment (intralesional excision, cryosurgery) may be anticipated.

Some reports in the literature, discussing the effect of cryosurgery on articular cartilage, are available.

In an effort to find an alternative for high condylectomy in the management of painful degenerative arthritis of the temporomandibular joint, Marciani et al performed a cryosurgical lesion of the mandibular condyle in monkeys[16]. The structure of bone remained intact, but the articular cartilage was irreversibly damaged.

Malawer et al demonstrated in an experiment using dogs, that cryosurgery can produce bone necrosis 7 to 12 mm away from the surface of the cavity being treated; this in contrast to the minimal zone of necrosis produced by the heat of polymerization of polymethyl-methacrylate[13]. Malawer et al found that cryosurgery had no effect on articular cartilage.

Aboulafia et al described a technique for treatment of large subchondral tumors of the knee[1]. Curettage, cryosurgery, and composite reconstruction with bone graft, cement, and osteosynthesis were 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, treated in the same fashion once again. All nine patients had an excellent functional outcome. Only two patients had mild degenerative changes of the knee.

Our experience suggests that articular cartilage can be damaged by cryosurgery[32]. This is in concurrence with the series of Sheth et al who reported fragmentation with carpal collapse in a group of patients with giant cell tumor located in the distal radius and treated by adjuvant cryosurgery[33]. Malawer et al reported on two patients with radiographic and clinical evidence of degenerative changes, out of a series of 48 patients with giant cell tumor located around the knee joint[15]. On the other hand, we have frozen articular cartilage several times in situations, which from the beginning point were unfavorably but as yet did not result in symptomatic osteoarthritis (Figure 3-6).
So it seems that articular cartilage can resist low temperatures to some degree. In practice, local control of the tumor (especially in case of an intra-articular pathological fracture) has priority, dealing with osteoarthritis seems in those circumstances of concern later[2].

DAMAGE TO NERVES

Nerve palsy is a complication of cryosurgery, which was recognized at the very early beginning of the introduction of cryosurgery for bone tumors. Marcove reported nine (most transient) nerve palsies in 128 patients all treated for various types of bone tumors[18,19,21,22].
If nerves are frozen, their function is only temporarily impaired. Most neuropraxias resulting from freezing will resolve in 6 weeks to 6 months[9]. 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. We do not use tourniquets, to keep nerves and skin vascularized and thereby to protect them from a freeze injury.

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Chapter 4

COMPLICATIONS IN CRYOSURGICAL TREATMENT OF BONE TUMORS; A RETROSPECTIVE STUDY OF 120 CASES

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Derived of:
Favourable results of cryosurgery in 120 patients with benign or low-grade malignant bone tumours. Nederlands Tijdschrift voor Geneeskunde 1999;143:2275-81

INTRODUCTION

Despite the promising reports of some pioneers in the field of cryosurgery, it did not become generally accepted as a local adjuvant to intralesional excision of active and aggressive benign, and low-grade malignant bone tumors[1,4]. Cryosurgery was, among other things, notorious for its high complication rate. In Chapter 3 it was established that this is unjustified. Those surgeons experienced in the cryosurgical technique, reach an acceptable complication rate. Since 1991 we have been using cryosurgery as a local adjuvant in the treatment of bone tumors. The surgical technique has generally been the same throughout this period. To evaluate our cryosurgical skills, we studied the complication rate in a retrospective study of 120 patients.

MATERIAL AND METHODS

A total number of 120 patients, with a minimum follow-up period of 1 year, were included in this retrospective study. Patients were treated with intralesional excision and adjuvant cryosurgery for various bone tumors. The histologically confirmed diagnoses in this group of patients were: aneurysmal bone cyst, simple bone cyst, enchondroma, borderline- and Grade 1 chondrosarcoma, chondroblastoma, giant cell tumor, eosinophilic granuloma and monostotic lesions of fibrous dysplasia. The average follow-up period was 36 months (13-103). Complications with subsequent treatment were evaluated. Only deep wound infections were taken into account.

A standardized technique was used in all cryosurgical procedures. The tumor was exposed through an oval window, about the length of the tumor. After curettage of the lesion, all remaining macroscopic tumor tissue at the margin of the lesion was removed with a high-speed burr. While monitoring the local temperature with needle-mounted thermocouples, three consecutive freeze/thaw cycles were performed with the use of a liquid nitrogen spray. A tourniquet was not applied, so blood perfusion could protect the skin and neurovascular bundle from thermal damage. The remaining defect was reconstructed, for which several techniques had been used, depending on the size and location of the tumor. In time, based on personal experience, we started to use titanium plate fixation in diaphyseal lesions of weightbearing bones and in metaphyseal lesions with severe bone loss, to prevent pathological postoperative fractures.

RESULTS

Of the 32 patients treated because of an aneurysmal bone cyst (ABC), two patients developed a local recurrence of the tumor. Both were successfully treated with a second cryosurgical procedure. Five times, a postoperative pathological fracture was encountered. Three patients with lesions, located in the distal tibia, the distal radius and the proximal humerus, sustained a fissure that had no further clinical implications. One patient, with a large lesion of the calcaneus, suffered from a deep wound infection and a gradual collapse of the calcaneal body, which resulted in osteoarthritis of the subtalar joint. The fifth patient sustained a posttraumatic

Figure 4-1. Routine radiograph of the right wrist of a 23-year-old woman with a recurrent giant cell tumor 5 months after curettage, adjuvant cryosurgery, and homologous bone grafting (A). One month after re-operation with intralesional excision, adjuvant cryosurgery, and homologous bone grafting, a fissure may be visible (B). Evident fracture (arrow) and extensive callus formation with some radial deformity 5 months after re-operation (C). Routine radiographs respectively 7 (D,E) and 14 months (F,G) after re-operation; fracture healing and early signs of radiocarpal osteoarthritis. This patient also suffered from a giant cell tumor around the right knee, 10 years before her wrist lesion, and is currently under treatment for a giant cell tumor, located in the right acetabulum.

femoral fracture after treatment of an aneurysmal bone cyst in the distal femur, and was treated with intramedullary nailing. Two superficial wound infections healed uneventfully in this group of ABC. One patient, with a lesion of the distal radius, had a transient nerve palsy of the superficial radial nerve. Two patients, one with a calcaneal lesion (as mentioned before) and one with a distal radial lesion (Figure 4-1), developed osteoarthritis. Twice, a mild growth deformity was noticed in lesions located in the distal tibia.

Thirteen patients were cryosurgically treated for simple bone cysts (SBC) because of persistence of the lesion after several steroid injections. Two local recurrences, which needed no further treatment but monitoring, were encountered. In one patient, a postoperative fissure healed uneventfully. One patient, treated for a humeral SBC, had a transient radial nerve palsy. One lesion, involving the proximal humeral growth plate, resulted in a growth disturbance of the arm (4 cm shortening).

Enchondromas, of which 21 were included in these series, showed a local recurrence in one case. Two patients with a fissure were treated with immobilization. Another two patients needed osteosynthesis for a postoperative fracture. All bony complications occurred in femoral lesions. One of the patients who needed osteosynthesis was primarily treated by cryosurgery, bone grafting, and plate fixation. One month after surgery, the plate was removed because of a deep wound infection, and 6 months later he sustained the pathological fracture.

Borderline and grade 1 chondrosarcomas showed no local recurrence after cryosurgical treatment. One patient sustained a postoperative fracture during a car crash, and was treated by plate fixation. Two other patients sustained a fissure of the distal femur and proximal humerus; both patients recovered well with non-operative treatment. A transient radial nerve palsy was seen in one patient with a grade 1 chondrosarcoma of the proximal humerus.

In the seven patients treated for chondroblastomas no complications were encountered.

Out of the 13 patients with a giant cell tumor (GCT), four times a local recurrence was observed. Recurrent lesions were treated with cryosurgery (two patients) or marginal excision (two patients). In one patient a postoperative fissure occurred and in another patient a deep wound infection was encountered. Transient nerve palsies were observed of the superficial radial nerve (lesion in the distal radius) and the peroneal nerve (lesion in the fibular head). In the latter case the peroneal nerve was entrapped by the tumor. A permanent nerve palsy of the sarcal roots was observed in a patient with a GCT of the sacrum (S1-2); he still suffers from faecal incontinence.

In the seven patients who had eosinophilic granuloma, no complications were observed except for one postoperative, pathological, subtrochanteric fracture, treated by plate fixation.

Twelve monostotic lesions of fibrous dysplasia showed one local recurrence after cryosurgical treatment. Two patients, with a postoperative fracture of the humeral diaphysis and the proximal femur, respectively, were treated conservatively. Fracture healing was uneventful.

In two out of the 120 patients included in these series, characteristic clinical phenomena of venous gas embolism were observed during the cryosurgical procedure. After abortion of the cryosurgical procedure the vital signs returned to normal within a few minutes.

Table 4-I summarizes the complications in our series. Postoperative fractures were observed at various time intervals after the cryosurgical treatment. In Figure 4-2 an overview is presented of the delay in mechanical failure. In halve of the patients with a postoperative fracture the bone failed within 6 weeks after the operation. The two patients with a delay of 65 and 156 weeks were involved in an accident.

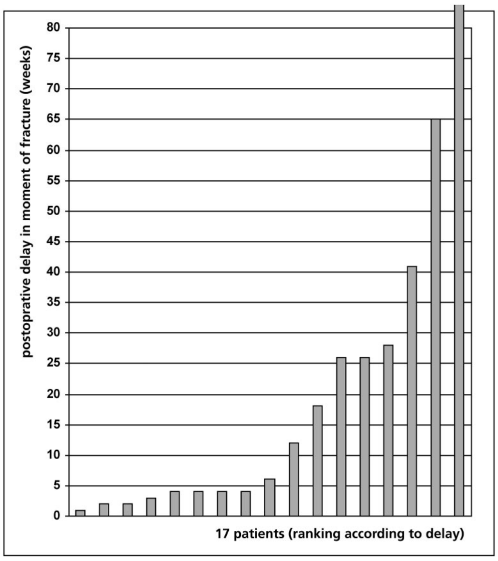

Figure 4-2. Time interval between the operation and the moment of fracture in the 17 patients whom sustained a postoperative fracture. The patients are ranked according to the time interval.

Table 4-I
Data of the 120 patients treated by cryosurgery, and the number of complications observed

Diagnosis	**Number of patients**	**Number of recurrences**	**Number of complications**				
			Fracture	*Infection*	*Nerve palsy*	*Osteo-arthritis*	*Growth disturbance*
ABC	32	2	5	3	1 (TNP)	2	2
SBC	13	2	1	-	1 (TNP)	-	1
Enchondroma	21	1	4	1	-	-	-
Borderline / grade 1 chondrosarcoma	15	-	3	-	1 (TNP)	-	-
Chondroblastoma	7	-	-	-	-	-	-
Giant Cell Tumor	13	4	1	1	3 (2 TNP)	-	-
Eosiniphilic granuloma	7	-	1	-	-	-	-
Fibrous Dysplasia, monostotic	12	1	2	-	-	-	-
Total	120	10 (8%)	17 (14%)	5 (5%)	6 (5%)	2 (2%)	3 (3%)

ABC= aneurysmal bone cyst; SBC= simple bone cyst; TNP= transient nerve palsy.

DISCUSSION

Local tumor control, the primary goal of adjuvant cryosurgery, was obtained. Except for those patients with giant cell tumors of bone, the local recurrence rate was low. Oncologic outcome after cryosurgical treatment of giant cell tumors of bone is discussed in detail in Chapter 9.
The incidence of deep wound infections in this series was acceptable and in concordance with other series reported in the literature (Chapter 3, Table 3-1). Surgical principles, as mentioned in Chapter 3, were deferred to. The occurrence of secondary osteoarthritis and growth disturbances was infrequent in these series. Nevertheless, one should take the detrimental effects of cryosurgery on the cartilage and the growth plate into consideration[2,3,5,6], at the same time realizing that local recurrence of the tumor might be devastating as well.
Palsies of the radial nerve, all of them transient, were frequent (four out of six palsies) in this study. Common radial nerve palsy is related to the treatment of humeral lesions, while superficial radial nerve dysfunction is related to the treatment of distal radial lesions. In the cryosurgical treatment of sacral tumors, sacral roots are at risk for permanent dysfunction. In our series, sacral roots were always encased by the tumor and therefore deliberately frozen.
In the present study the most frequently (14%) encountered complication of the cryosurgical treatment was a postoperative fracture. Eight out of 17 fractures occurred in femoral lesions, and halve of them needed operative treatment. There was a wide range in the moment of spontaneous failure. Early fractures might indicate that the quality of the remaining bone stock was misjudged at the beginning. But it is unknown whether the cryosurgical procedure contributes to pathological fractures at such a short period. Even so, it is unknown whether late (more than 12 weeks) fractures can be contributed to the cryosurgical procedure.
In conclusion, cryosurgery of active and aggressive benign, and low-grade malignant bone tumors results in good local tumor control with a moderate complication rate. The spontaneous, postoperative fractures are of concern. Adjustments have already been made by the application of preventive osteosynthesis in lesions at risk. Furthermore, experimental studies should be conducted to further study the role of cryosurgery in the mechanical failure of the bone.

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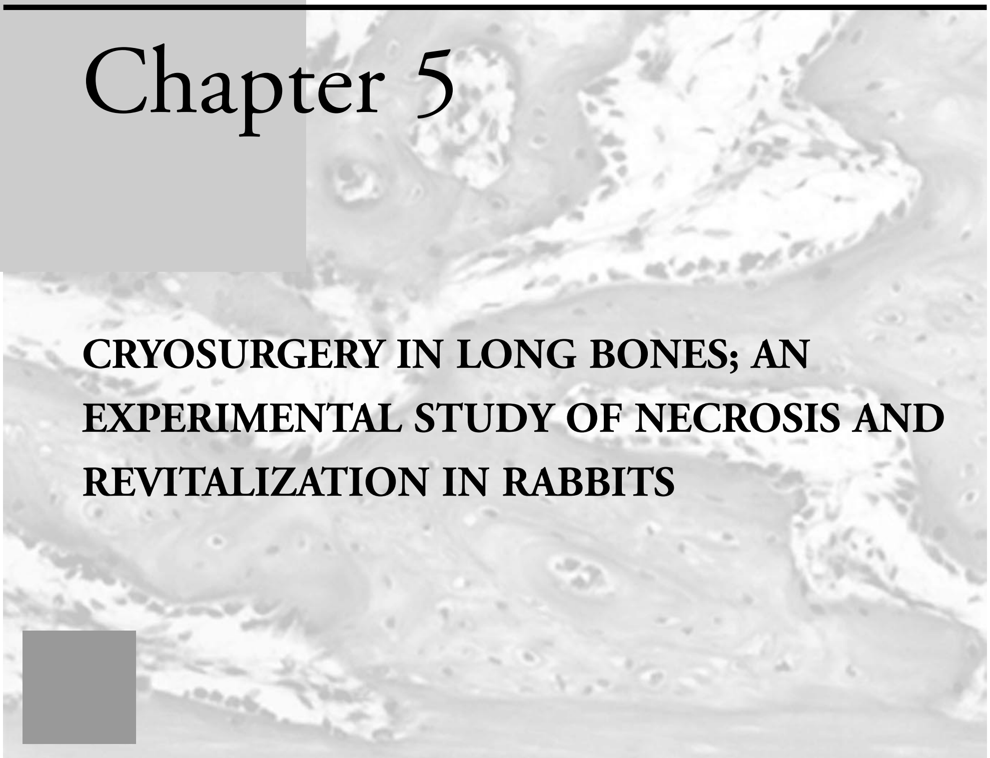

Chapter 5

CRYOSURGERY IN LONG BONES; AN EXPERIMENTAL STUDY OF NECROSIS AND REVITALIZATION IN RABBITS

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ABSTRACT

Cryosurgery is an established adjuvant treatment of bone tumors which reduces the local recurrence rate. In this study, cryosurgical experiments were carried out in rabbits to study the temperature field, the extent of necrosis and the revitalization process in order to optimize treatment. Intramedullary freezing of long bones with a closed liquid nitrogen cryoprobe and three consecutive sessions induces osteonecrosis down to the (-10°C isotherm without compromising the soft tissues. The application of a tourniquet does not influence thermodynamics. The revitalization process is distinguished into an osteogenic and a remodeling phase. In rabbits there is an obvious periosteal osteogenesis starting from 1 week after operation and overlapping the remodeling phase, which starts between 3 and 5 weeks after operation. Two out of eight rabbits sustained a pathologic fracture within 3 weeks of cryosurgery. No pathologic fractures were encountered during the remodeling phase, probably because of the profuse periosteal bone apposition that added mechanical strength. In clinical practice, no profound periosteal bone apposition and a high risk for pathologic fractures during the remodeling phase were noted. Future research should focus on bone strength during the remodeling phase of cryosurgical treated long bones, to decide on the role of preventive osteosynthesis or postoperative restrictions. This animal model is not advised for these biomechanical experiments because of its profuse periosteal bone apposition.

INTRODUCTION

In 1968 Gage and Erickson reported the use of cryosurgery as adjuvant treatment of bone tumors to achieve a reduction of the local recurrence rate[5]. After curettage of the bone tumor, tumor residue at and beyond the surgical margin may be responsible for tumor recurrence. Additional cryosurgical treatment of the surgical margin will induce osteonecrosis and destroy tumor residue. The calcified matrix of the osteonecrotic bone persists, maintaining the structural integrity of the bone.

Incomplete cryosurgical procedures may result in local tumor recurrence. Too vigorous freezing, on the other hand, will increase the risk of wound dehiscence, infection, and neurovascular lesion. Moreover, prolonged freezing will increase the area of osteonecrosis and the risk of pathologic fractures, because the revitalization process of the necrotic bone probably effects its mechanical strength[3]. In order to optimize the cryosurgical procedure and minimize the damage to the bone, it is necessary to know about the temperature field that develops around the bony cavity, the effect of tourniquet use, and the critical freeze temperature that causes cell death of bone and tumor tissue.

The purpose of this animal experiment was to study the cryosurgical temperature field, the effect of tourniquet use on freeze and thaw dynamics, the extent of necrosis, and the revitalization process. Two in vivo cryosurgical animal experiments were performed on long bones in rabbits. In the first one, both the effect of tourniquet use on the thermodynamics and the correlation between the cryosurgical temperature field and the extent of the necrosis were studied. In the second experiment, histological examination was performed to study the revitalization process.

MATERIALS AND METHODS

Temperature field and necrosis

Identical cryosurgical procedures were carried out bilaterally on the tibial bones of five New Zealand White rabbits. The animals received premedication with 0.5 mg atropine i.v. and were anesthetized with 0.15/10 mg/kg fentanyl/fluanison i.v. After intubation, general anesthesia was maintained with O_2/N_2O (35%/65%) and ethraan. On the left side, a tourniquet was applied. Under sterile conditions, the anterolateral tibial diaphysis was exposed to insert a closed liquid nitrogen cryoprobe (diameter 2 mm) into a hole drilled into the cortex. The cooling temperature of the probe was -150^{o}C when connected to a cryosurgical system (Erbokryo SN, ERBE Elektromedizin GmbH, Tübingen, Germany). The cryosurgical procedure and local temperature field were monitored with the use of five thermocouple needles (diameter 0.8 mm; copper/copper-nickel alloy; ELLAB A/S, Roedovre, Denmark) and real-time graphical visualization. The needles were positioned longitudinally in the cortex at 2, 4, 6, 8, and 10 mm distance from the edge of the probe at a depth of 3 mm (Figure 5-1). Temperature data were acquired with a digital multimeter (Digital multimeter 2000, Keithley Instruments, Cleveland OH, USA) equipped with a thermocouple scanner card (2001-TCSCAN, Keithley Instruments, Cleveland OH, USA) and stored in a database.

Three freeze/thaw cycles of 20 minutes were performed with a freeze time of 45 seconds and spontaneous warming up. The freeze time was defined as the period of liquid nitrogen supply to the cryoprobe and did not indicate the moment of maximum temperature drop at the freeze front. The effect of tourniquet application was studied by quantifying freeze and thawing

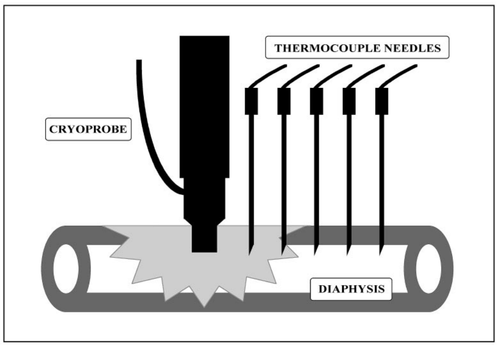

Figure 5-1. Schematic drawing of the experimental setup as used for measuring the temperature field in the tibial diaphysis of rabbits. Both cryoprobe (diameter 2 mm) and thermocouple needles (diameter 0.8 mm) are press-fit positioned in cortical drill holes at 2, 4, 6, 8, and 10 mm distant from the edge of the cryoprobe.

dynamics. Because cooling rate, minimum freeze temperature, duration of the freeze period, and thawing rate are all important parameters in causing cell death, the area above the temperature-time curve is used for quantifying both freeze and thaw dynamics (Figure 5-2) [16]. The Levene's test for equality of variance confirmed a normal distribution of data. The paired *t*-test was used for comparing thermodynamics with or without tourniquet application. The level of significance was α=0.05.

The animals were killed 1 week after operation. The tibial bones were excised, roentgenographed, and fixed in 4% formaldehyde solution. The bone was decalcified (ethylene

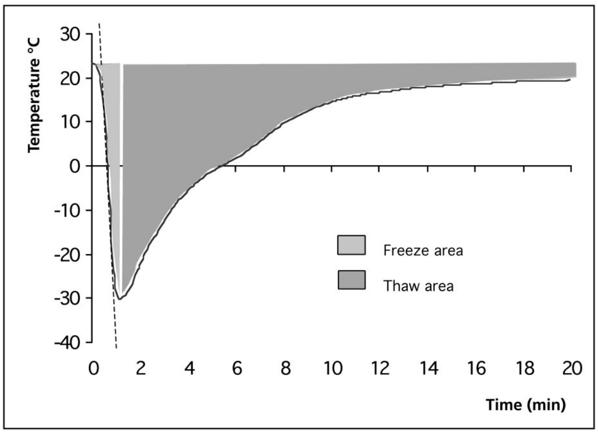

Figure 5-2. Temperature registration of the first freeze/thaw cycle of the left tibia in rabbit no. 4 with application of a tourniquet. Temperature measured by the thermocouple needle positioned at 4 mm distant from the edge of the cryoprobe. *Dotted line* delineates the maximum cooling rate. Freeze and thawing dynamics are quantified separately by the area above the temperature-time curve.

diamine tetraacetic acid, EDTA), imbedded in polymethylmethacrylate (PMMA), and sectioned for hematoxylin and eosin staining. The extent of necrosis was evaluated in relation to the temperature field.

Table 5-I
Experimental data of the study on revitalization in eight rabbit femora (unilateral experiments)

Rabbit number	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Roentgenographed at (week)	1	3	3	3	3	3/6	3/6/9	3/6/9/12
Killed at (week)	1[a]	3	3	3	5	7	9	12
Fracture	-	-	+	+	-	-	-	-

[a] Died 1 week after operation because of respiratory complications.

Revitalization.
The experiment was carried out unilaterally on femoral bones of eight New Zealand White rabbits. Under general anesthesia and sterile conditions, the lateral femoral diaphysis was exposed. Care was taken not to jeopardize the periosteum with its vascularization. The cryoprobe (diameter 2 mm) was press-fit positioned in a drill hole with only one thermocouple needle at 4 mm distance from the edge. Three freeze/thaw cycles of 10 min each were performed. For each cycle, the freeze time was adjusted in order to reach a minimum temperature of -10°C at the location of the thermocouple needle. The animals were not restricted in their activities, neither was the leg protected. The animals were killed at 1, 3, 5, 7, 9, and 12 weeks after surgery (Table 5-I). Two rabbits sustained a pathologic fracture and were replaced by new animals, making a group of eight rabbits. The femoral bones were excised, roentgenographed, and prepared for histological examination as mentioned before.

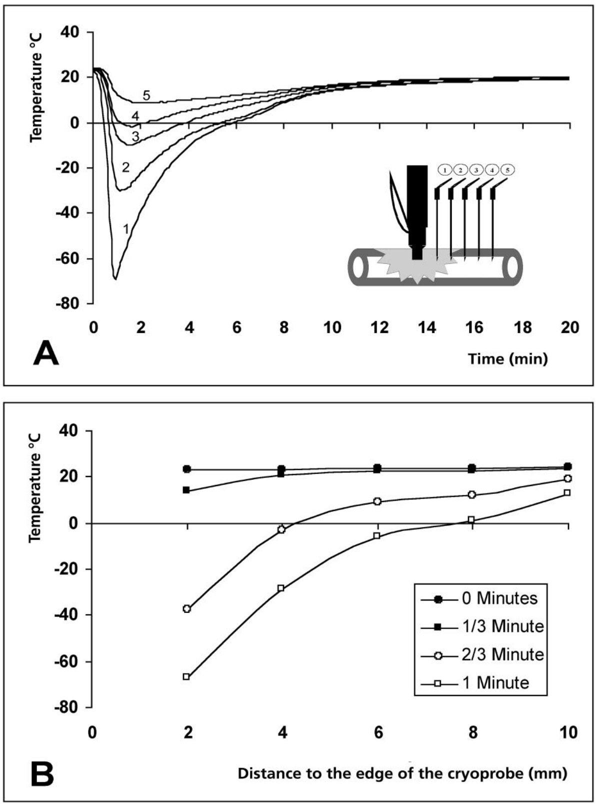

Figure 5-3 A,B. The first freeze/thaw cycle of the left tibia in rabbit no. 4 with application of a tourniquet. Five thermocouple needles at 2, 4, 6, 8, and 10 mm distant from the edge of the cryoprobe are used. Temperature-time curve (A). The freeze time was 45 s. At close range, there was a more profound temperature drop and cooling rate (temperature drop per minute). Temperature-distance curve (B). Measurements at 0, 1/3, 2/3, and 1 min after the start of the freeze session. An exponential relation was observed between temperature and distance from the cryoprobe.

RESULTS

Temperature field and necrosis.

In all cryosurgical sessions, thermocouple needles close to the cryoprobe registered a greater cooling rate (temperature drop per minute), than more distantly positioned needles (Figure 5-3A). A nonlinear relation between temperature drop and distance to the cryoprobe was observed: Approaching the edge of the cryoprobe, there was an exponential drop in the temperature (Figure 5-3B).

Temperature data registered by the thermocouple needle positioned at 4 mm distance from the edge of the cryoprobe were used for studying the effect of tourniquet application on thermodynamics. Data are listed in Table 5-II. Comparing the area above the temperature-time curve, there was no significant influence of tourniquet application on either freeze or thaw dynamics (p=0.56 and p=0.098, respectively).

One week after cryosurgery, histological examination revealed clear demarcation of the osteonecrosis with a circular shape. The osteonecrosis coincided with the -10°C isotherm as could be reconstructed with the help of peroperative temperature measurements by the five thermocouple needles. Necrotic cortical bone was characterized by empty lacunae and intravascular stasis. Periosteum covering the necrotic bone and adjacent viable cortex showed a profound reaction with apposition of woven bone.

Table 5-II
Temperature data measured by the thermocouple needle at 4 mm distance from the edge of the cryoprobe. On the left leg, a tourniquet was applied. Each leg sustained three freeze/thaw cycles of 20 min with a freeze time of 45 s and spontaneous warming up

Rabbit number	**1**		**2**		**3**		**4**		**5**	
Tibia	***Left***	***Right***	***Left***	***Right***	***Left***	***Right***	***Left***	***Right***	***Left***	***Right***
Minimum temperature(°C)										
Average of 3 cycles	-28	-32	-21	-17	-46	-30	-32	-29	-34	-32
SD	2.1	0.6	1.2	3.2	5.0	0.6	3.2	1.2	1.0	2.6
Cooling rate (°C/min)										
Average of 3 cycles	98	114	47	47	138	105	104	101	112	124
SD	25	16	3	5	9	10	6	4	5	27
Freeze area (°C.min)										
Average of 3 cycles	25	26	39	34	36	31	31	34	29	33
SD	1	8	7	2	3	4	4	3	2	3
Thaw area (°C.min)										
Avarage of 3 cycles	264	263	258	221	278	249	243	231	232	212
SD	37	39	55	21	25	33	28	21	28	22

Revitalization.
Rabbit 6 died of a postoperative respiratory complication 1 week after operation (Table 5-I). Wound healing was without complications. Two rabbits (8 and 9) sustained a pathologic spiral-type fracture within 3 weeks after operation and were replaced by new ones.
In all cases, roentgenographs of the femoral bones made 3 weeks after operation demonstrated an obvious periosteal reaction at and beyond the cryosurgical lesion. The width of this reaction was two to three times the thickness of the cortex.
Histological examination of the femoral bones revealed a sharply demarcated, circular- shaped necrosis of the cortex and bone marrow around the drill hole of the cryoprobe. The border of osteonecrosis coincided with the -10°C isotherm. Except for little fibrous scar tissue covering the cryolesion, the surrounding soft tissues did not show signs of necrosis, inflammation or degeneration. An endosteal and a profounder periosteal reaction was observed as early as 1 week after operation (Figure 5-4A). Lifting of the periosteum by the formation of well vascularized woven bone extended from the drill hole to far beyond the border of the cryolesion. Five weeks after operation, the endosteal and subperiosteal woven bone had partly remodeled, leaving more compact lamellar bone with the formation of a cavity with normal medullary tissue. The remodeling process of the necrotic cortex started at the periphery of the cryosurgical lesion between 3 and 5 weeks after operation. This was a process of creeping substitution with activity from both osteoclast and osteoblast forming so called *cutting cones*. Twelve weeks after surgery, the sharp border between necrotic cortex and periosteal/endosteal lamellar bone apposition was not completely remodeled by the creeping substitution (Figure 5-4B). At this time, most of the necrotic matrix was still in situ.

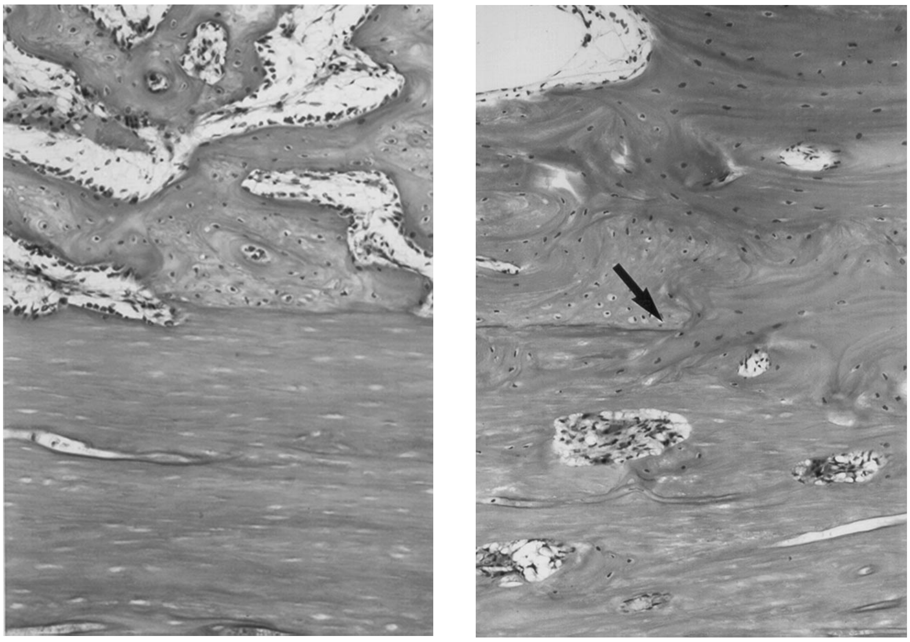

Figure 5-4. Hematoxylin and eosin-stained sections of rabbit femora (X140). Three weeks after operation, there was a marked periosteal reaction with the formation of woven bone, covering the necrotic cortex and adjacent diaphysis (**A**). After 12 weeks, the woven bone was completely remodeled to lamellar bone (**B**). The original cortical lining (*arrow*) was interrupted by the creeping substitution process.

DISCUSSION

This animal study demonstrated that a cryosurgical lesion in long bones can be achieved by a minimal surgical exposure with intramedullary freezing using a closed liquid nitrogen cryoprobe. Wide skin flaps, as recommended when applying a liquid nitrogen spray or a direct pouring technique, are not necessary [1,7,10,20].

In our study, temperature-time curves were characterized by high cooling rates and gradual thawing which, e.g., depended on the distance to the cryoprobe. This fast freezing and gradual spontaneous thawing in multiple cycles enhanced the cytotoxity [16]. The temperature field of cryosurgery in bone tissue has not been described before, but temperature-time and temperature-distance curves of identical configuration are reported for perfundated uterus tissue[19]. The use of a tourniquet did not affect freeze and thaw dynamics of cortical bone.

Three freeze/thaw cycles with a freeze temperature of -10°C induced osteonecrosis in our study. Cytotoxic temperatures of 0°C have been reported for dog femoral bones with the use of a liquid nitrogen direct poor technique [4]. This difference in cytotoxic temperature may be due to the various cryosurgical techniques used, each with its own cytotoxic capacity.

Periosteal and muscular tissue covering the osteonecrotic area showed no necrosis or degeneration in our study. Probably there is a temperature gradient at the diaphyseal border because of a higher blood perfusion rate in periost and muscle tissue. This assumption can not be confirmed because temperature field measurements at the border were not performed in this study. In the clinical application of intramedullary cryosurgery, this temperature gradient may provide a safety margin for adjacent neurovascular structures. This study did not deal directly with the oncologic issue of bone tumors because normal bone tissue instead of tumor tissue was frozen. Whether a cytotoxic temperature of -10°C, as found in our study, will guarantee tumor control remains the question. In vitro cryosurgical studies advise a –50° to -60°C freeze temperature in order to achieve adequate cancer cell death, thereby suggesting the need for more vigorous freezing to guarantee tumor control than was executed in our experiment [6,11,15]. Starting from the fundamental idea that tumor cells are more sensitive to cryosurgery than normal cells, this is in contrast to our present results [10,13,14]. According to the nonlinear temperature-distance relation found in this study, only 2 mm within the osteonecrotic border the temperature did reach -50°C, creating an oncologic safe margin.

After demarcation of the osteonecrotic diaphyseal cryolesion, our study showed an overlapping osteogenic and remodeling phase at histologic examination, in accordance with other experimental cryosurgical studies [1,2,4]. We found a remarkable strong osteogenesis at the periosteal site in rabbits starting as early as 1 week postoperatively. Within weeks, the periosteal woven bone had remodeled into lamellar bone. Kuylenstierna, in contrast to others, described regeneration of new bone from the marrow cavity without periosteal osteogenesis when freezing rabbit mandibulae [1,3,4,9,17]. This study demonstrated a long-term remodeling process of creeping substitution starting between 3 and 5 weeks after surgery at the periphery of the osteonecrotic lesion. Two rabbits sustained a pathologic fracture within three weeks after operation, probably due to the drill hole rather than the bone remodeling, which had not yet started.

Thus, in intramedullary freezing of long bones with a closed liquid nitrogen system and minimal surgical exposure, a freeze temperature of -10°C will mark the osteonecrotic front. Considering the temperature field registrations, this front will approximately coincide with an oncologically safe margin. Of special concern in clinical practice is the high percentage of pathologic fractures after the cryosurgical treatment of bone tumors, perhaps necessitating preventive osteosynthesis in the future[8,12,18]. The remodeling process of the necrotic cortex is supposed to weaken the bone, but in our rabbit study it did not result in pathologic fractures. This is probably because of the profuse periosteal bone apposition. Future experimental research on bone strength during the remodeling phase of cryosurgically treated long bones is necessary to decide on the role of preventive osteosynthesis or postoperative restrictions. For this purpose, we do not recommend the cryosurgical model in rabbits because of its profound periosteal bone apposition, which is not observed in clinical practice and which will influence bone strength.

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Chapter 6

BONE STRENGTH AFTER CRYOSURGERY OF LONG BONES; AN EXPERIMENTAL STUDY IN THE GOAT

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ABSTRACT

We investigated bone strength of cryosurgically treated diaphyseal gap defects with time and studied the relationship with the remodelling process. A randomised, unilateral experiment was performed of the femoral diaphysis in goats. Thirty-one animals received cryosurgery at the margin of a standardised, cylindrical gap defect. Another 31 animals (controls) received only the gap defect. At different time intervals up to 26 weeks, animals were sacrificed for mechanical testing in torsion, Computed Tomography and histological examination.

A significantly lower bone strength was measured at 4, 7, and 10 weeks after cryosurgery compared to controls. Bone density of the cryosurgically treated margin was significantly lower throughout the follow-up period and corresponded to areas of active cortical bone remodelling. Apposition of bone at the cryosurgical lesion was delayed compared to controls; at 4, 7, and 10 weeks the amount of bone apposition was significantly lower.

Cryosurgery reduces bone strength between 4 and 10 weeks postoperatively in the femur of goats, as compared to controls. This can be explained by the remodelling process of the necrotic cortex, which results in a longstanding increase in porosity. Besides, cryosurgery results in a delay of apposition of new bone at the site of the lesion, which otherwise would have contributed to bone strength, counteracting the negative effect on the mechanical strength of the increased porosity.

INTRODUCTION

Active and aggressive benign bone tumours compromise the structural integrity of bone by bone destruction and may lead to a pathological fracture. When treated intralesionally by curettage, a local adjuvant therapy like phenolization, polymethylmethacrylate packing or cryosurgery is advised to extent the surgical margin to achieve adequate tumour-control. Cryosurgery is known for its good cytotoxic capacity[14]. However, spontaneous post-operative fractures are frequently reported after adjuvant cryosurgical treatment in bone tumours[7-9,13].

A good understanding of bone behaviour after cryosurgery is necessary to decide on the need for reconstructive procedures of the remaining defect at operation. However, few animal experiments deal with the issue of loss of bone strength after cryosurgical treatment[5,10].

To study the effect of cryosurgery on bone strength we performed an in vivo experiment in the goat. In a cryosurgical model of the femoral diaphysis, the remodelling process of the lesion and the torsional bone strength were evaluated up to 26 weeks post-operatively. The study was based on three questions: does cryosurgery of long bones reduce their bone strength; if so, at what time interval; and can loss of bone strength be explained by the remodelling process of the necrotic bone?

MATERIAL AND METHODS

Operation technique

An unilateral experiment was performed on 62 skeletally mature Dutch milk goats (Capra Hircus Sana). After premedication with intravenous 0.5 mg atropine, general anaesthesia was induced by intravenous 0.15/10 mg/kg fentanyl/fluanison and maintained via endotracheal intubation with O_2/N_2O (34%/65%) and ethraan (1%). Each animal was randomised for both type and side of operation. Under routine sterile conditions, the femoral diaphysis was exposed using a straight lateral approach and leaving the periosteum unattended. At a distance of 80 mm from the knee, a standardised gap defect was created in the lateral cortex with a cylindrical diamond drill (diameter 4.5 mm; Diamond Bone Cutting System, Merck Biomaterial, Darmstadt, Germany). A needle-mounted thermocouple (copper and copper-nickel alloy; diameter 0.8 mm; ELLAB A/S, Roedovre, Denmark) was placed in the cortex at 5.75 mm from the lining of the defect for continuous registration of local temperature.

In the 31 animals that served as a control group (Group II) the wound was closed in layers at this point. Another 31 animals (Group I) received adjuvant cryosurgical treatment at the margin of the defect, using a closed liquid nitrogen cryosurgical system (Erbokryo SN, ERBE Elektromedizin GmbH, Tübingen, Germany). Three freeze/thaw cycles of 15 minutes each were performed with a cryoprobe, press fit positioned in the cortical defect. For each cycle the freeze time was adjusted in order to reach a minimum temperature of $-10^{\circ}C$ at the location of the thermocouple needle, creating a circumferential osteonecrotic margin of 6 mm wide[6].

The present model was based on pilot experiments in rabbits[6] and goats. The pilot studies showed that the osteonecrosis-front extended up to the $-10^{\circ}C$ isotherm, and that spontaneous postoperative fractures were frequent (75%) in the goat if a gap defect (diameter 5 mm) with a cryosurgical margin of 10 mm was used. To prevent spontaneous fractures, the cryosurgical margin was reduced to 6 mm in this study.

The animals were not restricted in their activities neither was the leg protected. In both groups, four animals were sacrificed at each time intervals of 0, 13, 16, and 24 weeks, and five animals at each time intervals of 4, 7, and 10 weeks. Paired femora were excised and stored at $-30^{\circ}C$. Muscle and periosteum, covering the defect, were left unattended in connection with the Computed Tomography and histological examinations. All paired specimens were used for radiographic, Computed Tomography and mechanical analysis, whereas two samples of each time interval were assessed histologically.

Radiographic and Computed Tomography analysis

Routine anteroposterior and lateral radiographs of the test femora were taken postoperatively and postmortem to exclude gross disease.

A postmortem transverse Computed Tomogram, with a slice thickness of 1mm was made at the centre of the cortical defect (Stratec XCT-960A, Stratec Medizintechnik GMBH, Birkenfeld-Gräfenhausen, Germany). The current authors looked for differences in geometry of the femoral diaphysis between Group I and Group II for each time interval. By coloured graphical visualisation, differences in density and their geographical distribution were depicted. Bone density was expressed as mg Ca^{2+}/cm^3 and determined with a voxel size of 0.087 mm^3.

Cortical bone density of the margin of the defect was measured in 6 adjacent square regions (measuring 2.5 mm^2) as shown in Figure 6-1. A threshold value of 1100 mg Ca^{2+}/cm^3 was used. To exclude partial volume effects, the regions did not communicate with the periosteal or endosteal lining of the cortex. Region A, together with region B and C were considered as representative for the cryosurgically induced osteonecrotic margin (Figure 6-1).

To quantify the bridging of the cortical gap defect and the apposition of new bone tissue, we measured the area of bone within a radius of 6.3 mm, using a threshold value for trabecular bone (530 mg Ca^{2+}/cm^3)(Figure 6-1).

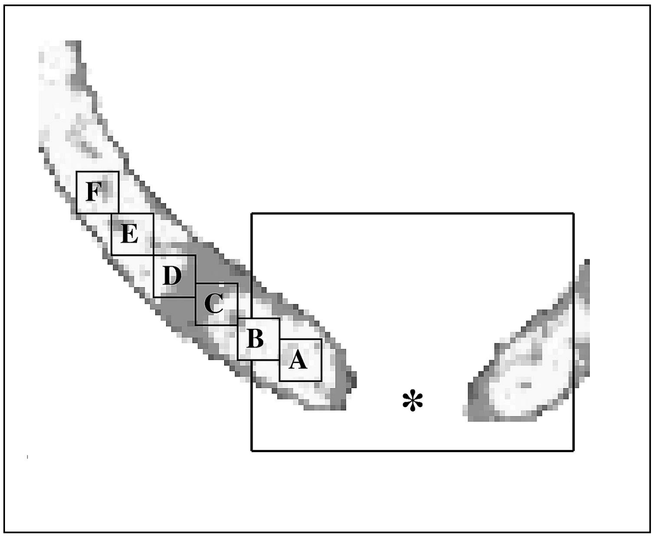

Figure 6-1. Detail of a transverse computed tomogram 7 weeks postoperatively. Darker toned gray corresponds to lower bone density. Asterisk shows the center of the cortical defect and the demarcated region of 12.6 mm width in which the area of bone is measured. Six adjacent square regions (A up to F) of 2.5 mm^2 subdivide the margin of the defect.

Mechanical testing

Both operated and contralateral femurs were embedded in acrylate (AutoPlast, Candulor AG, Wangen, Switzerland), so that a diaphyseal segment of 6 cm length, with the defect located in the centre, was tested. Throughout the experiment, the specimens were kept moist with Ringers lactate (0.9%) at a room temperature of 20°C. The specimens were mounted in a Materials Testing System machine (MTS SYSTEMS GMBH, Berlin, Germany), in which the distal mold was loaded in exotorsion and the proximal mold was fixated except for axial translation (Figure 6-2). All femora were tested in torsion to failure at a rate of 2°/second. The results of torque versus deformation angle were plotted on a graph. The parameter chosen to reflect torsional strength was torque at failure. Torsional strength of the operated femur was expressed as a percentage of torque at failure, versus the contralateral specimen of the same animal.

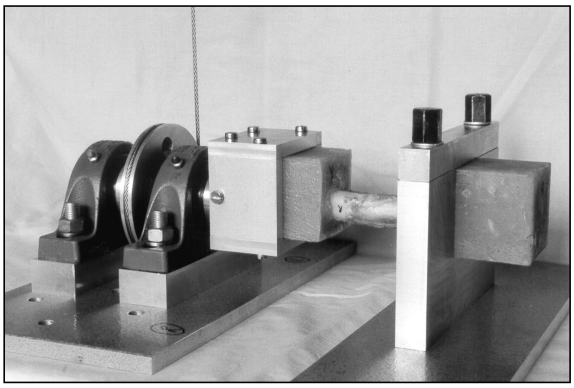

Figure 6-2. Picture of an embedded specimen in the test equipment. This equipment was mounted in a MTS testing machine. The torsion axis was parallel and in the center of the femoral diaphysis at the level of the defect. The distal mold was loaded in exorotation at a rate of 2 degrees per second.

Histological analysis
At each time intervals 4, 7, 10, 13, 16, and 26 weeks, two specimens of Group I were evaluated histologically. The fractured specimens were reconstructed as far as possible after the mechanical test and cut in the sagital plane at the level of the former defect. The fatty bone marrow, which was separated from the overlying cortex during the mechanical failure, was not used for histological evaluation. After fixation in 4% formaldehyde solution and decalcification in 25% ethylenedinitrilotetraacetic acid disodium salt dihydrate, the bone was embedded in polymethylmethacrylate. Multiple sections of each specimen were taken to minimise inadequate sampling. Sections were stained with haematoxylin and eosin (HE) and examined for extent of necrosis, remodelling of the necrotic bone, apposition of new bone tissue, and signs of infection.

Statistical analysis
Results are presented as means with their sample standard deviations after each time interval for both treatment groups. It is examined for each of the groups whether between 0 and 16 weeks the course of the means can be described by a linear trend or a quadratic curve on the basis of a saturated two-way analysis of variance model (SAS procedure GLM). To avoid bias due to loss of data the observations at 26 weeks have been excluded from this analysis. As regards torque ratio in the cryosurgery group, only the means from 4 weeks have been modelled. Separate contrast tests were performed to compare both groups at each time interval, and to compare the torque ratio means in the cryosurgery group between 0 and 4 weeks.

RESULTS

The goats tolerated the operative procedure well. The gait pattern normalised at the second post-operative day, and no wound healing problems were observed.
Three goats in the cryosurgery group sustained a spontaneous spiral fracture of the operated femur, at 45, 61, and 62 days post treatment; two of them were to be evaluated at 26 weeks and one was to be evaluated at 13 weeks. Data of these specimens were lost for all further analysis. There was no significant difference between both groups with respect to the occurrence of spontaneous fractures, when using the chi-square test ($p=0.24$).
In Group I, one contralateral specimen of the 4 weeks time interval was lost for mechanical testing due to structural damage during post-mortem processing. In Group II, one contralateral and one operated specimen of the 26 respectively 10 weeks time interval were damaged during post-mortem processing and lost for mechanical testing.

Radiographic and Computed Tomography analysis
Lateral radiographs of the cryosurgically treated specimens (Group I) showed a radiolucent zone around the defect, extending up to the position of the needle-mounted thermosensor. This zone was most clearly observed at 7 weeks post treatment.
Outer bone diameter and cortical thickness of the diaphysis measured the same in both groups for each time interval.
On gross appearance, Computed Tomograms of the cortical defects in Group I showed a local decrease in bone density at the cryosurgical margin with time. At 4 weeks, the first decrease of bone density at the periphery (region C) was noted, as well as the periosteal and endosteal side of

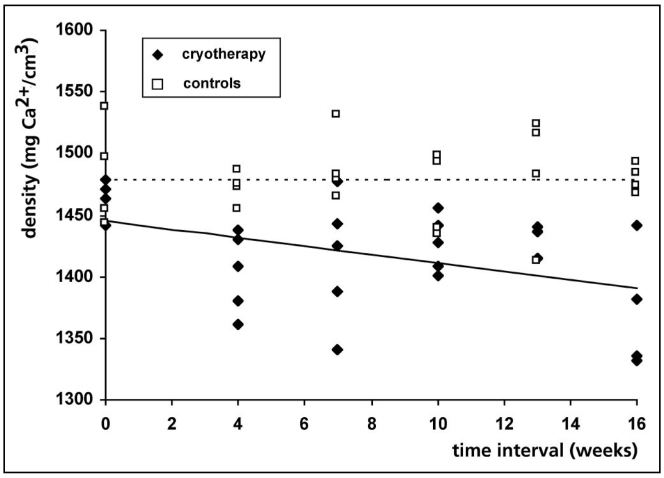

Figure 6-3: Bone density observations of the combined regions A-B-C for Group I and II at different time intervals post treatment. The solid c.q. dotted line represents the theoretical course of the mean value y as a function of week w for the cryotherapy treatment (y=1444.91-3.38w) respectively the control treatment (y=1478.83+0.01w).

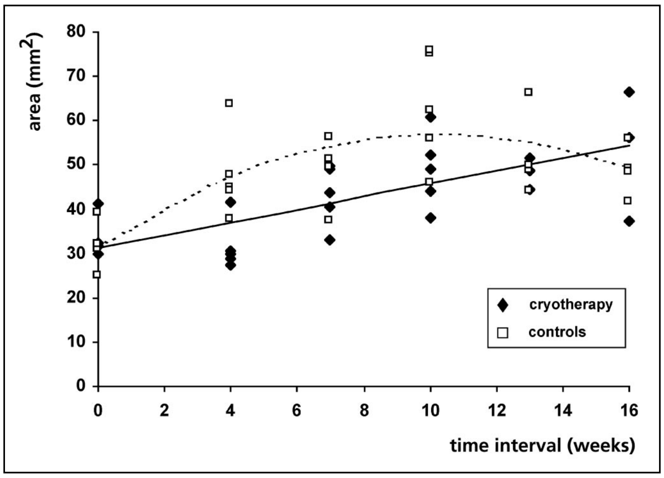

Figure 6-4. Bone apposition observations at the gap defect for Group I and Group II at different time intervals post treatment. The solid c.q. dotted line represents the theoretical course of the mean value y as a function of week w for the cryotherapy treatment (y=31.18+1.46w) respectively the control treatment (y=31.05+4.98w-0.24w^2).

Table 6-I

Data of the mechanical experiment and the Computed Tomography analysis

Time interval (weeks)	**Torque at failure (Nm)**		**Percentage torque versus contralateral**		**Bone density (mg Ca^{2+}/cm^3)**		**Bone area (mm^2)**	
	Group I	***Group II***	***Group I***	***Group II***	***Group I***	***Group II***	***Group I***	***Group II***
0	65 ± 15 [4]	51 ± 13 [4]	77 ± 9 [4]	77 ± 10 [4]	1464 ± 16 [4]	1483 ± 43 [4]	34 ± 5 [4]	32 ± 6 [4]
4	65 ± 8 [5]	68 ± 7 [5]	73 ± 1 [4]	88 ± 16 [5]	1403 ± 33 [5]	1472 ± 11 [5]	32 ± 6 [5]	48 ± 10 [5]
7	67 ± 12 [5]	78 ± 16 [5]	79 ± 6 [5]	103 ± 3 [5]	1415 ± 52 [5]	1484 ± 27 [5]	43 ± 7 [5]	49 ± 7 [5]
10	79 ± 10 [5]	91 ± 15 [4]	87 ± 13 [5]	106 ± 6 [4]	1427 ± 23 [5]	1473 ± 33 [5]	49 ± 9 [5]	63 ± 13 [5]
13	82 ± 14 [3]	76 ± 12 [4]	93 ± 8 [4] 1)	93 ± 8 [4]	1431 ± 14 [3]	1484 ± 51 [4]	48 ± 4 [3]	52 ± 10 [4]
16	78 ± 17 [4]	84 ± 16 [4]	105 ± 14 [4]	99 ± 9 [4]	1373 ± 51 [4]	1479 ± 11 [4]	54 ± 12 [4]	49 ± 6 [4]
26	98 ± 24 [2]	98 ± 9 [4]	95 ± 3 [2]	102 ± 7 [3]	1355 ± 41 [2]	1455 ± 39 [4]	55 ± 14 [2]	47 ± 5 [4]

The values represent the mean ± SD. [ ]= number of specimens measured; Group I= cryotherapy; Group II= controls; 1)= after substitution of 81.37 for the missing value.

the osteonecrotic lesion. This area corresponded to the radiolucent zone on the lateral radiographs. By 16 weeks, the osteonecrotic lesion as a whole (combined region ABC) showed loss of bone density. Bone density of the combined region ABC remained constant with time in the control group (Figure 6-3). Means with their standard deviations are presented in Table 6-I.
A linear course of bone density with time for both groups can be accepted (p=0.30). There is a significantly decreasing course with time for the cryosurgery group (p=0.01). Cryosurgically treated specimens have a significantly (p<0.001) lower bone density at 4, 7, 10, 13, and 16 weeks.
In both groups, the area of bone in the region of the defect generally increased with time (Table 6-I). The controls initially showed a rapid increase in bone area, but this changed into a decrease later on. Cryosurgically treated specimens showed a gradual increase throughout the follow-up period (Figure 6-4).
A linear course for Group I and a quadratic course for Group II can be accepted (p=0.30). There is a significantly increasing course with time for the cryosurgery group (p<0.001). The amount of bone apposition is significantly lower for the cryosurgically treated specimens at 4, 7, and 10 weeks (p<0.002).

Mechanical testing
All specimens showed a linear pattern on the torque versus angular displacement curves up to the moment of failure. The mechanical test leaded to a multi-fragmental spiral fracture, involving the remaining cortical defect in the operated specimens.
The results regarding torque at failure and percentage torque at failure are shown in Table 6-I. At 0 weeks, the percentage torque was dropped to about 80% in both groups due to the operation. With time, the decreased percentage torque recovered (Figure 6-5).

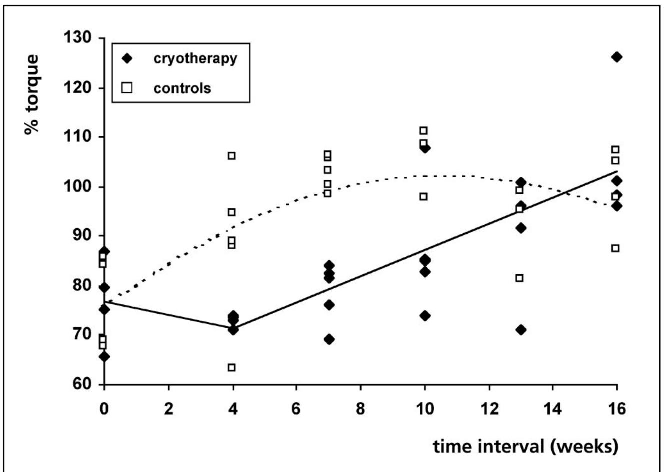

Figure 6-5. Bone strength observations for Group I and Group II at different time intervals post treatment. The solid c.q. dotted line represents the theoretical course of the mean value y as a function of week w for the cryotherapy treatment (y=76.83 for w=0, y=71.46+2.63(w-4) from w=4) respectively the control treatment (y=75.83+4.90w-0.228w^2).

To avoid bias, the percentage torque value of one specimen in Group I, that sustained a spontaneous fracture and was planned for the 13 weeks time interval, was substituted by the lowest value observed for this time interval. A linear course from week 4 for Group I and a quadratic course for Group II can be accepted (p=0.38). There is a significantly increasing course with time for the cryosurgery group (p<0.001). The percentage torque at failure was significantly reduced in cryosurgically treated specimen at 4, 7, and 10 weeks (p<0.001),

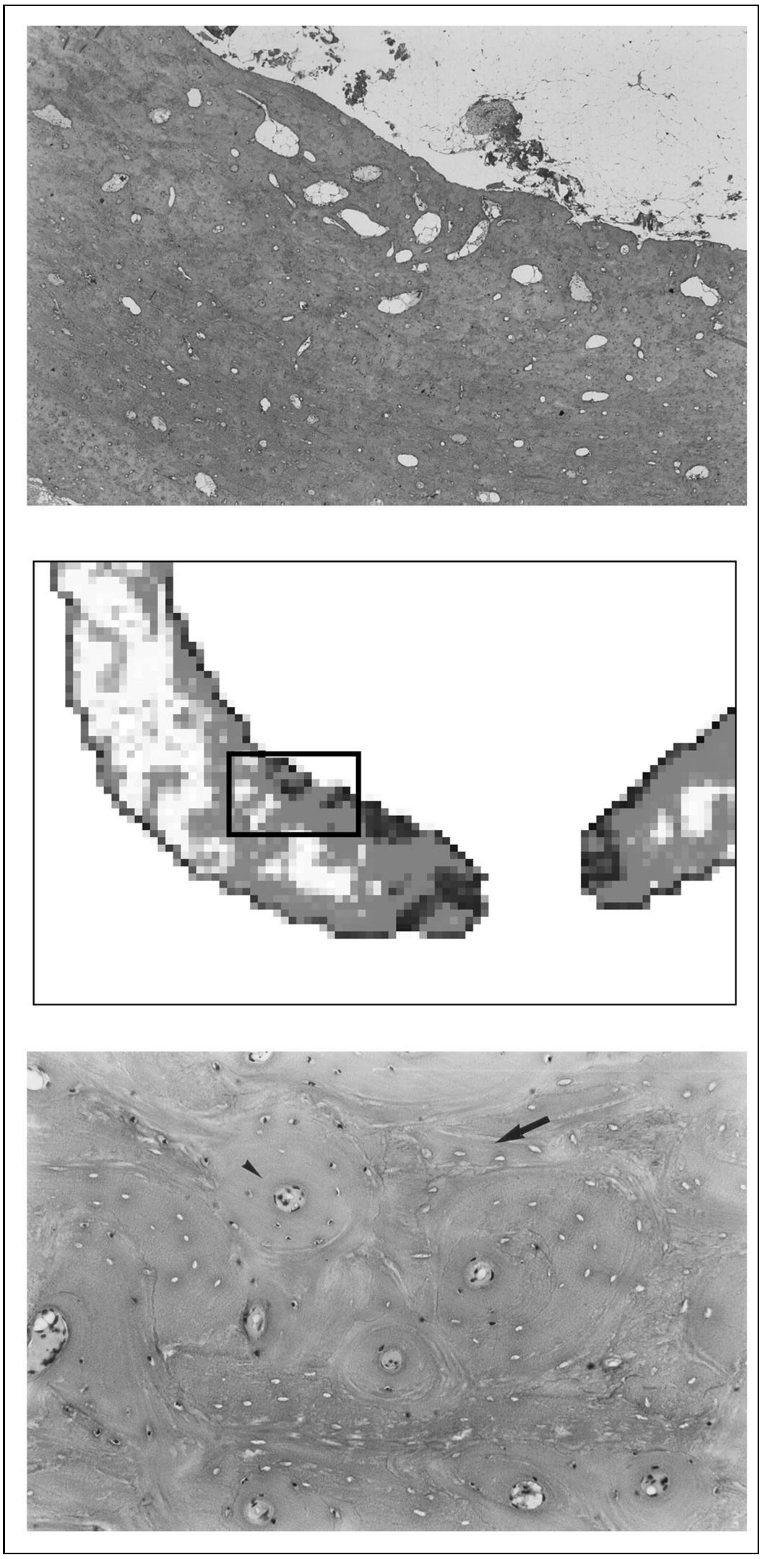

Figure 6-6. Area of revascularization with osteoclast enlargement of the haversian canals at the endosteal site of the osteonecrotic lesion 13 weeks after cryotherapy; HE stained section X25 (A). The resulting lacunae show up as a region of lower bone density (darker gray) at the corresponding Computed Tomogram (B). Detail of remodelled osteons (arrow head) in between original necrotic interstitial lamellae (arrow); HE stained section X200 (C).

compared to controls. No significantly lower mean was found (p=0.37) after 4 weeks compared to week 0 within the cryosurgery group.

Histological analysis

Histological examination of Group I revealed necrosis of the cortex at the margin of the cryosurgically treated defect. There were no signs of low-grade infection.

Both periosteum and endosteum, covering the osteonecrotic lesion were viable, as they showed a reaction at the 4 weeks time interval, extending from the defect to far beyond the borders of the lesion. Immature woven bone, lifting of the periosteum and endosteum, was especially formed at the periosteal lining. The woven bone was remodelled to lamellar bone by 16 weeks, forming a sleeve of compact bone around the osteonecrotic lesion.

The osteonecrotic margin of the defect underwent a remodelling process of creeping substitution; new bone formation (osteoblast activity) was preceded by revascularization and osteolysis (osteoclast activity), which resulted in the formation of lacunae (*cutting cones*). This creeping substitution started at 4 weeks at the adjacent viable cortex as well as the periosteal and endosteal border. At 16 weeks, the remodelling front reached the centre of the osteonecrotic lesion. Approximately one-half of the pre-existing necrotic matrix was still in situ at 26 weeks. At that moment, the unrepaired matrix was most of all confined to the interstitial lamellae. Figure 6-6 shows an example of the histological picture with corresponding computed tomogram, 7 weeks post treatment. The region of remodelling coincides with the region of decreased bone density.

The histological features of the cryosurgically treated cortical gap defect are summarised in Figure 6-7 in relation to the follow-up period.

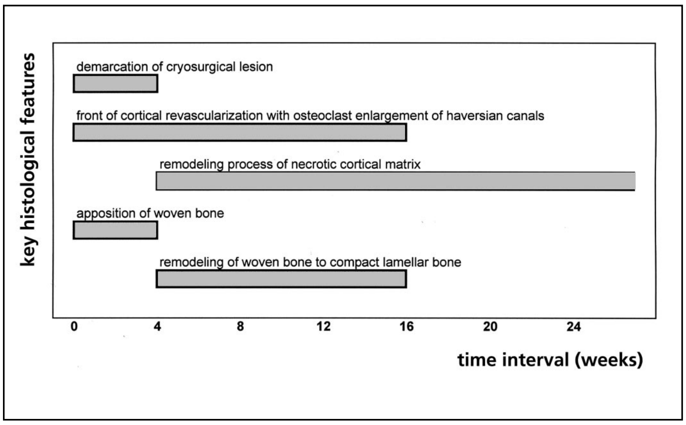

Figure 6-7. Key histological features, observed after cryotherapy of the lining of a cortical gap defect in the goat, in relation to the follow-up period.

DISCUSSION

Bone strength reduction

Three cryosurgically treated animals sustained a spontaneous spiral fracture at approximately 2 months post treatment, versus none of the control animals. Spiral type fractures occur in torsion, and are attributed to failure in tension[1,12]. Gage, one of the pioneers of cryosurgery, already warned for the risk of pathological fractures due to cryosurgical treatment[4]. In his animal study he described 11 spontaneous spiral fractures out of 26 dog femora, usually close to or in the third month after cryosurgery. In contrast with our model, Gage used a large cryosurgical lesion the size of the total diaphyseal circumference. For obvious reasons larger lesions will give more reduction of bone strength.

It is not the cryosurgical procedure itself that compromises bone strength, as our study did not reveal a loss of bone strength immediately post treatment. Rapid freezing with a closed liquid nitrogen probe, resulting in the rapid expansion of trapped liquid with possible crack propagation, did not lead to significant weakness of bone[11].

With time, our study showed a reduction of torsional bone strength of the femora that were treated by cryosurgery, compared to the control femora. Sufficient data were available to study the time period up to 16 weeks postoperatively. The reduction was significant at 4, 7, and 10 weeks. To the author's knowledge only 2 experimental studies deal with the issue of bone strength reduction after cryosurgical treatment[3,10]. In both studies, the mandibles of Lister rats were treated with a closed liquid nitrogen probe. They reported a significant reduction at 8 weeks post treatment, using a three point bending test without a proper control group. Our study has more clinical relevance for orthopaedic practice because of the skeletal segment, the concomitant gap defect and the mechanical test we used. Besides, we used a larger laboratory animal with per-operative temperature monitoring so that the disturbing effect of variation in the surgical procedure could be minimised.

Remodelling process

The revitalisation process accounts for the mechanical weakening of cryosurgically treated long bones with time. Bone density of the osteonecrotic lesion was significantly lower with than without cryosurgery at 4 weeks post treatment and throughout the follow-up period. Data at 26 weeks were insufficient for statistical analysis, but suggest a prolonged reduction of bone density. This lower density is a reflection of increased porosity due to an initial wave of revascularization and osteoclast enlargement of the haversian canals. In time, the spaces are narrowed again by osteoblasts that refill the space with osteoid (remodelling by creeping substitution). An end-point of remodelling is not reached at 26 weeks time. This remodelling process is analogous to the remodelling reported of massive cortical autografts. Experimental studies on the physical behaviour of massive cortical autografts showed a correlation between increased porosity of the matrix and decreased bone strength[2,5]. Thus, increased porosity of the matrix is one explanation for the mechanical weakening that takes place from the fourth until the tenth weeks post treatment.

The surgical procedure, with or without adjuvant cryosurgery, gives cause for a healing response resulting in sub-periosteal, and to a lesser extent sub-endosteal, apposition of immature woven bone. Remarkable is the fact that cryosurgery in itself will not prevent the periosteum and endosteum to react with the formation of woven bone. Our study shows a delay in bone apposition if cryosurgery is applied. The amount of bone apposition was significantly less for cryosurgically treated femoral gap defects at 4, 7, and 10 weeks postoperatively. This is probably related to damage to the osteoinductivity of these layers. Remodelling of the immature periosteal and endosteal bone to lamellar bone leaves a sleeve of bone that counteracts the weakening of the osteonecrotic lesion due to the resorptive osteoclast activity. This explains why the prolonged porosity of the osteonecrotic lesion does not result in a proportional longstanding weakening. In this model, periosteal bone apposition is probably the most important determinant of torsional bone strength, since significant differences between both groups were observed in the same period (4 – 10 weeks) for bone apposition as well as percentage torque. Literature reports some arguments that plead in favour of the mechanical role of an appositional bone sleeve. McCord, in his experimental study on the effects of ceramics on the strength of bone subjected to cryosurgery, reported that hyperplasia of immature sub-periosteal woven bone results in increased bone strength[10]. Another argument comes from Enneking's work on physical aspects of repair in dog massive cortical autografts[2]. In his study, the plane of mechanical failure of the graft seems to be dictated by the plane that intersected the least amount of bone apposition.

The answers to the questions posed in the "Introduction" are that cryosurgery does reduce bone strength, that this mechanical weakness is present between 4 and 10 weeks postoperatively in the goat, and that this can be explained by delayed bone apposition together with the remodelling process.
Extrapolation of the quantitative data of this animal experiment to clinical practice is not justified. But our study gives more clarity in the biological processes that takes place after cryosurgical treatment of bone and what implications that may have for its structural integrity. We advise prophylactic osteosynthesis of cryosurgically treated bone tumours, especially those located in the diaphysis, for remodelling of the necrotic cortex is attended by a longstanding weakening through increased porosity. Carefulness is required in handling the periosteum and in preventing spill of liquid nitrogen, for the apposition of bone is an important determinant in the recovery of the structural integrity of the bone.

ACKNOWLEDGEMENTS

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Chapter 7

THE ROLE OF BONE GRAFTING IN THE HEALING OF CRYOSURGICALLY TREATED BONE DEFECTS; IN VIVO EXPERIMENTS ON GOAT FEMORA

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Clinical Orthopaedics and Related Research. Under review.

ABSTRACT

The influence of cancellous bone grafting on the healing of cryosurgically treated gap defects of long bones was investigated. A unilateral in vivo experiment was done to study bone strength and graft incorporation in the goat. The lining of a cylindrical defect of the femoral diaphysis was treated with a closed liquid nitrogen cryoprobe in 62 goats. Thirty-one animals received an impacted morselized cancellous bone graft harvested from the sternum. The other 31 animals served as controls. At 0, 4, 7, 10, 13, 16, and 26 weeks animals were sacrificed to test torsional strength, computed tomography, and histologic assessment. Specimens with a bone graft showed no significant increase in torsional strength in time compared with the controls. Resorption of the bone graft occurred within 10 weeks after treatment. The amount of bone apposition at the site of the cryosurgical lesion and the moment of bridging of the defect were similar in both groups. Cancellous bone grafting does not accelerate healing of cryosurgically treated, stable diaphyseal defects in the goat. Lack of mechanical loading, probably more than cryosurgically induced compromised perigraft environment, accounts for the failure of the graft.

INTRODUCTION

Cryosurgery is used as a local adjuvant after intralesional resection of benign and low-grade malignant bone tumors[19,20]. After curettage of the tumor with subsequent cryosurgery of the lining of the cavity, a defect remains, but the continuity of the bone is preserved. Several options for reconstruction of the defect are available: a cancellous bone graft, a massive cortical strut graft, internal fixation, polymethylmethacrylate, or a combination of these. Cancellous bone grafting is used routinely for reconstruction, especially in young patients where a biologic reconstruction is preferred. The purpose is enhancement of the healing process. To some extent, a cancellous bone graft also contributes to primary stability of the lesion. By this effect, the rehabilitation period will be shortened and the risk for postoperative fractures will be reduced. Clinical or experimental studies that support the beneficial role of bone grafting in cryosurgically treated bone tumors are not available to the authors' knowledge. Necrosis of the surgical margin of the tumor, induced by cryosurgery, will jeopardize revascularization of the bone graft. Because revascularization of the graft is a prerequisite for incorporation, the beneficial effect of bone grafting in restoring mechanical integrity of the bone can be questioned[13,23].

To study the role of cancellous bone grafting in the healing rate of cryosurgically treated bony defects in long bones, the authors performed an in vivo experiment in the goat. Bone graft incorporation and torsional bone strength were evaluated at various intervals up to 26 weeks in a cryosurgical model of the femoral diaphysis. The authors questioned whether cancellous bone grafting accelerates healing of a cryosurgically treated defect in long bones.

MATERIAL AND METHODS

Operation technique

A unilateral experiment was done on 62 skeletally mature Dutch milk goats (Capra Hircus

Sana). After premedication with intravenous 0.5 mg atropine, general anesthesia was induced by intravenous 0.15/10 mg/kg fentanyl/fluanison and maintained via endotracheal intubation with O_2/N_2O (34%/65%) and ethraan (1%). Under routine sterile conditions, the lateral femoral diaphysis was exposed, leaving the periosteum unattended. At a distance of 80 mm from the knee, a standardized circular defect was created in the lateral cortex with a cylindrical diamond drill (diameter 4.5 mm; Diamond Bone Cutting System, Merck Biomaterial, Darmstadt, Germany). A needle-mounted thermocouple sensor (copper and copper-nickel alloy; diameter 0.8 mm; ELLAB A/S, Roedovre, Denmark) was placed in the cortex at 5.75 mm from the lining of the defect for continuous registration of local temperature.
Cryosurgery of the margin of the defect was done with a closed liquid nitrogen probe (Erbokryo SN, ERBE Elektromedizin GMBH, Tübingen, Germany), press-fit positioned in the cortical defect, and using three consecutive freeze/thaw cycles of 15 minutes. For each cycle, the freeze time was adjusted to reach a minimum temperature of 10ºC at the location of the thermocouple sensor, creating a circumferential osteonecrotic margin of 6 mm wide[9].
In the 31 animals that served as a control group (Group II), the wound was closed at this point. In the other 31 animals (Group I), the cortical defect was filled with impacted morselized autologous bone graft, harvested from the sternum just before the operative procedure on the femur. Under sterile circumstances, the cancellous chips (wet weight, 0.6 mg) were made into a cylinder (diameter 4.5 mm and length 9 mm) using a hammer and custom-made impactor.
The animals were allowed unrestricted ambulation. In both groups, four animals were euthanized at 0, 13, 16, and 24 weeks and five animals were euthanized at 4, 7, and 10 weeks. At sacrifice, paired femurs were excised and stored at -30ºC. Muscle and periosteum covering the defect were left unattended to integrate densitometric and histologic examinations. All paired specimens were used for computed tomography (CT) and mechanical evaluation, whereas two specimens of each interval were assessed histologically.

Radiographic and computed tomography analysis
Routine anteroposterior (AP) and lateral radiographs of the test femurs were taken postoperatively and postmortem to exclude gross disease and to evaluate bridging of the defect. A postmortem transverse CT (Stratec XCT-960A, Stratec Medizintechnik GMBH, Birkenfeld-Gräfenhausen, Germany) with a slice thickness of 1 mm was made, focused on the center of the cortical defect. The current authors looked for differences in geometry of the femoral diaphysis between Group I and Group II for each interval. By colored graphic visualization, geometry of the specimen and distribution of bone densities could be evaluated. This allowed study of the fate of the bone graft and the cryosurgical lesion in time. Bone density was determined with a voxel size of 0.087 mm^3 and expressed as $mgCa^{2+}/cm^3$.
Incorporation of the bone graft, together with apposition of new bone tissue at the osteonecrotic cortical margin, was quantified by measuring the area of bone within a radius of 6.3 mm from the center of the defect and using a threshold value of 530 $mgCa^{2+}/cm^3$ (Figure 7-1).

Mechanical testing
Operated and contralateral femurs were embedded using acrylate (AutoPlast, Candulor AG, Wangen, Switzerland), so that a diaphyseal segment of 6 cm, with the defect located in the center, was tested. Throughout the experiment the specimens were kept moist with Ringers lactate (0.9%) at a temperature of 20ºC. The specimens were mounted in a Materials Testing System machine (MTS SYSTEMS, Berlin, Germany), in which the distal mold was loaded in

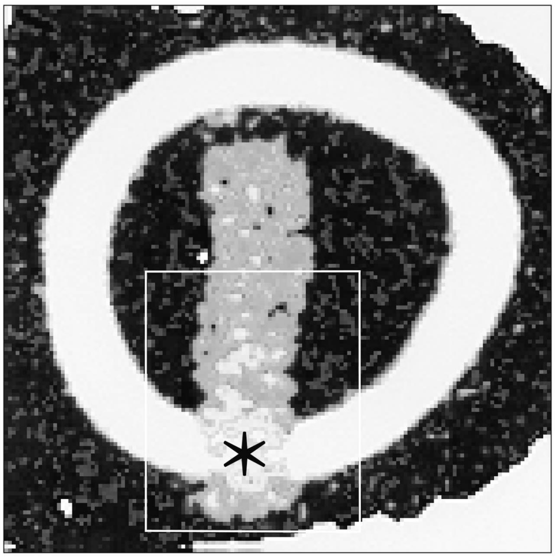

Figure 7-1. Example of a transverse computed tomogram at 0 weeks postoperatively. Darker toned gray corresponds to lower bone density. The area of trabecular and cortical bone was measured at the lateral hemisphere of the diaphysis, within a square region of 12.6 mm width, and using a threshold value of 530 mgCa^{2+}/cm^3. Asterisk shows the impacted cancellous bone graft within the cortical defect.

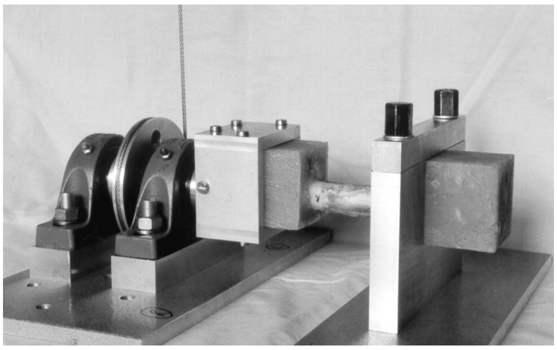

Figure 7-2. Picture of an embedded specimen in the test equipment. This equipment was mounted in a MTS machine. The torsion axis was parallel and in the center of the femoral diaphysis at the level of the defect. The distal mold was loaded in external rotation at a rate of 2 degrees per second.

external rotation and the proximal mold was fixated except for axial translation (Figure 7-2). All femurs were tested in torsion to failure at a rate of 2º/second. The results of torque versus deformation angle were plotted on a graph. The parameter chosen to reflect torsional strength was the percentage torque at failure versus contralateral.

Histologic evaluation

At 4, 7, 10, 13, 16, and 26 weeks, two specimens of both groups were evaluated histologically. The specimens were reconstructed after the mechanical test, and cut in the sagittal plane at the level of the former defect. After fixation in 4% formaldehyde solution and decalcification in 25% ethylenedinitrilotetraacetic acid disodium salt dihydrate, the bones were embedded in polymethylmethacrylate. Multiple sections of each specimen were taken to minimize inadequate sampling. Sections were stained with hematoxylin and eosin (HE) and examined for signs of infection, extent of necrosis, remodeling of the necrotic bone, apposition of new bone tissue, and incorporation of the bone graft with healing of the defect.

Statistics
Results are presented as means, with standard deviation. A two-tailed T-test with Bonferroni correction was used to compare both groups for each interval.

RESULTS

The goats recovered after the operative procedure, showing normal gait patterns and no wound healing problems. In both groups, one contralateral specimen (at 4 and 13 weeks in Group II and Group I, respectively) was lost for mechanical evaluation because of structural damage during postmortem processing. Three goats in Group II were lost for evaluation because of a spontaneous fracture of the surgically treated femur at 45, 61, and 62 days postoperatively; two of the goats were to be evaluated at 26 weeks and one goat was to be evaluated at 13 weeks. Using the chi-square test, there was no significant difference between both groups concerning the occurrence of spontaneous fractures (p=0.24).

Radiographic and computed tomography analysis
Routine lateral radiographs of the surgically treated specimens revealed a radiolucent zone around the defect, extending to the location of the needle-mounted thermosensor. This zone, coinciding with the cryosurgical margin, was the clearest observed between 4 and 16 weeks postoperatively. The defect showed complete healing in three specimens in Group I (at 16 and 26 weeks), and in one specimen in Group II (at 26 weeks). The bone grafts used lost their density with time. At 10 weeks, no remnants of the grafts were observed on the lateral radiograph.

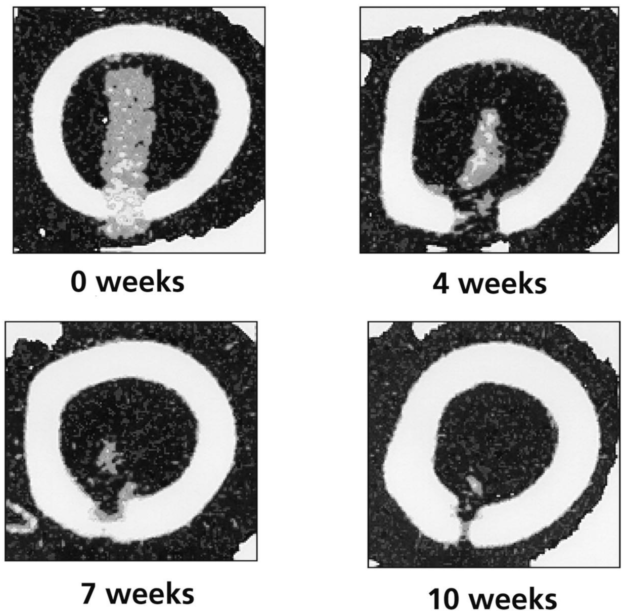

Figure 7-3. Computed tomograms of representative specimens at 0, 4, 7, and 10 weeks postoperatively showing the evolution of the bone graft with time. At 10 weeks, most of the bone graft had been resorbed.

Table 7-I
Data of the mechanical experiment and Computed Tomography analysis

Time interval (weeks)	Torque at failure (Nm)		Percentage torque		Bone area (mm^2)	
	Group I	*Group II*	*Group I*	*Group II*	*Group I*	*Group II*
0	57.0 ± 5.1 [4]	64.7 ± 14.5 [4]	80.3 ± 5.3 [4]	76.8 ± 7.7 [4]	75.3 ± 4.8 [4]**	33.8 ± 4.3 [4]**
4	61.0 ± 12.8 [5]	64.5 ± 8.4 [5]	75.0 ± 9.2 [5]	72.9 ± 1.1 [4]	66.5 ± 14.6 [5]*	31.6 ± 5.0 [5]*
7	71.7 ± 11.2 [5]	66.5 ± 11.6 [5]	90.3 ± 16.2 [5]	78.7 ± 5.4 [5]	59.2 ± 5.7 [5]*	43.2 ± 6.2 [5]*
10	81.5 ± 6.2 [5]	78.7 ± 9.6 [5]	80.0 ± 13.3 [5]	87.0 ± 11.3 [5]	52.8 ± 2.6 [5]	48.8 ± 7.6 [5]
13	68.5 ± 12.2 [4]	82.2 ± 13.7 [3]	92.8 ± 3.5 [3]	96.2 ± 3.8 [3]	56.0 ± 1.4 [4]	48.2 ± 2.9 [3]
16	81.6 ± 6.9 [4]	77.5 ± 17.0 [4]	110.5 ± 10.1 [4]	105.4 ± 12.2 [4]	65.5 ± 18.5 [4]	54.0 ± 10.4 [4]
26	95.8 ± 19.8 [4]	98.1 ± 23.7 [2]	100.8 ± 4.9 [4]	95.3 ± 1.9 [2]	57.2 ± 8.4 [4]	55.2 ± 9.8 [2]

The values represent the mean ± SD; [ ] = number of specimens measured; Group I = cryosurgery; Group II = controls; * $p<0.05$; ** $p<0.005$.

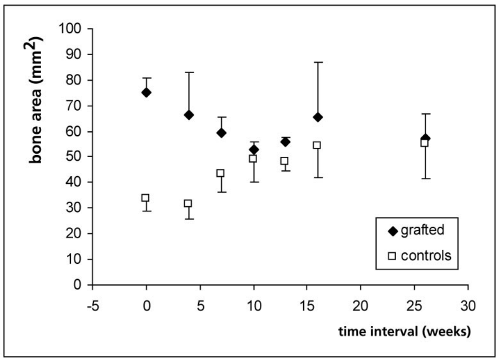

Figure 7-4. Bone apposition at the cryosurgically treated defect for Group I and Group II with time. Bone apposition is expressed as the area (mm^2) of bone with a density greater than 530 $mgCa^{2+}/cm^3$ on the CT scans. At 0, 4, and 7 weeks, a significantly larger amount of bone was observed in the specimens that received a bone graft compared with controls. Values indicate the mean ± SD.

As in routine radiographic examination, CT scans of the defects in Group I showed resorption of the bone grafts within approximately 10 weeks postoperatively. Figure 7-3 shows some examples of the grafts on CT scans.

The cryosurgical margin of the defect showed a decrease in bone density in both groups, in accordance with the radiolucent zone on the radiographs. Density dropped in a uniform fashion, starting at the periphery of the osteonecrotic zone and then gradually extending toward the center. In time, bone apposition in both groups was observed predominantly at the periosteal site to a similar extent. Data of the quantitative assessment of the bone graft and the local bone apposition, expressed as area bone tissue, are listed in Table 7-I. At 0, 4, and 7 weeks, the amount of bone tissue at the cryosurgical defect was significantly higher in Group I (Figure 7-4).

Mechanical testing

When loaded in torsion, all specimens failed through the occurrence of a multifragmental spiral type fracture, involving the cryosurgical defect. The torque versus angular displacement curves showed a linear pattern up to the moment of failure.

Data of the mechanical experiment are listed in Table 7-I. Bone strength, expressed as percentage torque at failure versus contralateral, dropped to approximately 80% because of the surgery. Bone strength recovered with time (Figure 7-5). At 13 weeks, the percentage torque nearly reached the preoperative level of 100%. There were no significant differences in bone strength between both groups for any interval (p>0.25).

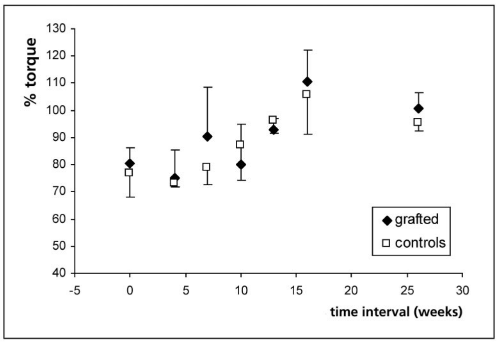

Figure 7-5. Bone strength for both groups, expressed as percentage of torque at failure versus contralateral, with time. At each interval, no significant difference was found between grafted specimens and controls (p>0.25). Values indicate the mean ± SD.

Histologic evaluation

The bone grafts showed uniform resorption the first 10 weeks after surgery. Remnants of the bone grafts appeared grossly loose and were lost for histologic examination when the specimens failed in the mechanical test. Of the three specimens in Group I showing complete radiographic bridging of the defect, one specimen was evaluated histologically at 16 weeks. Only a few necrotic remnants of the bone grafts, incorporated into viable compact bone, were observed (Figure 7-6). There were no other histologic features that could discriminate between the grafted specimens and the controls.

All specimens of both groups showed some fibrosis of the soft tissues directly overlying the cryosurgical region. Signs of infection only were seen in one specimen; histologic sections of a grafted specimen at 26 weeks had a few graft remnants located in the intramedullary canal that were surrounded by lymphocytes. Reaction of the periosteal lining, and to a lesser extent the

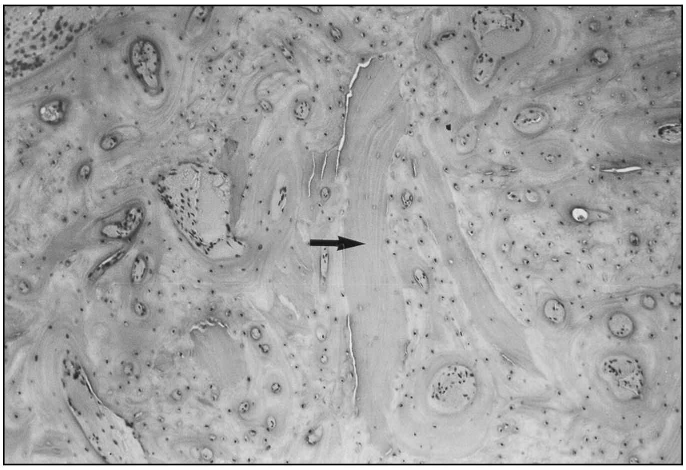

Figure 7-6-A. Area of the former defect, showing bridging at 16 weeks by viable compact bone; (A) small necrotic remnants of the bone graft (arrow) are incorporated into viable bone (stain, hematoxylin and eosin; magnification, X100).

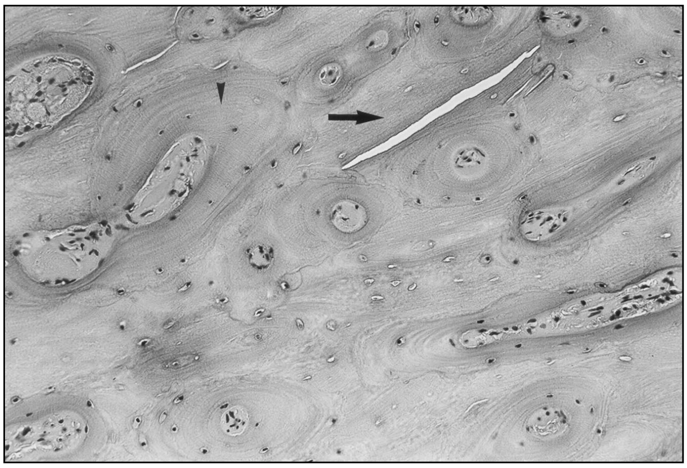

Figure 7-6-B. (B) The necrotic cortical lining of the former defect is partly remodeled, showing an admixture of necrotic (arrow) and viable (arrow head) osteons with enlarged haversian canals, *cutting cones* (stain, hematoxylin and eosin; magnification, X140).

endosteal lining, resulted in the apposition of woven bone at 4 weeks postoperatively. Apposition was confined to the osteonecrotic cortex and the surrounding viable cortex. At 16 weeks, this woven bone had been remodeled into compact lamellar bone, forming a sleeve of bone around the osteonecrotic lesion with progressive bridging of the defect.

At 4 weeks, the cryosurgical margin was demarcated by necrosis of the cortex lining the defect. Confined to each osteon, revascularization of the osteonecrosis with osteolytic widening of the haversian canals (*cutting cone* formation) preceded new bone formation. This process of remodeling (*creeping substitution*) was started 4 weeks after treatment at the periphery of the osteonecrotic margin, and extended like a front toward the center of the area, reaching the center at 16 weeks. The extension of the remodeling front on histologic examination was in accordance with the local decrease in cortical bone density at CT examination. By the end of 26 weeks, not all haversian canals regained their normal morphologies; approximately 1/2 of the former necrotic bone matrix still was evident.

DISCUSSION

The question for the experimental study was whether cancellous bone grafts will accelerate the healing process of cryosurgically treated, contained bony defects in long bones. Bone grafting commonly is used when aggressive benign and low-grade malignant bone tumors are treated by curettage and adjuvant cryosurgery. However, the efficacy of grafting for this purpose has not been clarified, as there is no algorithm for the type of defects which should be grafted. One matched clinical study stressed the beneficial use of cancellous grafts in the management of large, aggressive primary jaw lesions[16]. The risk of complications such as postoperative fractures was decreased, but the numbers reported were too small for statistical analysis. One could question the relevance of this study in jaw lesions, when dealing with tumors of long bones. Malawer et al[13] emphasized the detrimental effects of cryosurgery on the incorporation of bone grafts. The experimental study in dogs showed no incorporation of structural autologous cancellous grafts in bony defects treated with cryosurgery[13]. However, the study group was too small for statistical analysis.

The current study showed no beneficial effect of bone grafting. Torsional bone strength was not enhanced at any interval. Neither routine radiographic examination nor quantitative CT analysis showed incorporation of the impacted cancellous bone graft.
Reports on the incorporation of cancellous bone grafts are numerous. Biologic events occur during the process of incorporation in a uniform fashion[1]: (1) hematoma formation and an inflammatory reaction, (2) ingrowth of capillaries and repopulation of the graft by primitive mesenchymal cells, (3) osteoblasts lining the graft and depositing osteoid, and (4) osteoclasts resorbing necrotic donor bone. Autologous cancellous grafts are preferred, as they incorporate rapidly[1,2,3]. Likewise, homologous morselized cancellous grafts show near complete incorporation at 12 weeks when applied for impacted acetabular and femoral reconstructions in the goat[18,21]. This rapid incorporation of morselized bone graft in the goat was confirmed by Lamerigts et al[11].

The environment of the bone graft is extremely important for the success or failure of the graft[1,22]. Vascularity of the graft bed is one of the factors that plays a major role in bone graft incorporation, as is the presence of endothelial cells with their specific mitogens[3]. Cryosurgical treatment of a gap defect in the femur induces cell death and vascular thrombosis of the margin[4,9,10,14,17]. Therefore, the perigraft environment is attenuated and the graft probably fails to revascularize and incorporate. This hypothesis cannot be confirmed by the current study. There must be revascularization of the bone graft, because resorption is observed within 10 weeks. The findings contradict the conclusions of Malawer et al regarding the fate of a structural cancellous bone graft in a cryosurgically treated defect of a dog femoral condyle[13]. In the study of Malawer et al[13], the graft appeared grossly loose and showed no signs of incorporation up to 8 weeks postoperatively.

Local mechanical environment is another factor that influences graft incorporation. Stability of the graft with intimate contact is a prerequisite for revasularization, new bone formation, and host-graft union[1,5,11,22]. In addition, cyclic loading will stimulate remodeling of bone grafts which are incorporated, as it will promote fracture healing[1,6,7,8,11,15]. It is unknown whether the graft in the current model shared load. Because the drill hole in the femur only minimally jeopardizes the rigidity of the femur, the graft is stress shielded, causing unloading of the graft with resorption during the incorporation process as a result, as was the case in the current study. The hypothesis of unloading of the graft is inconsistent with the work of Lindsey et al[12]. They had sound incorporation of morselized autogenous bone grafts in an elongated gap defect of a canine femur. At 12 weeks, routine radiographic examination showed complete bridging of the defect without resorption of the graft.

In clinical practice, cryosurgery is used for various benign and low-grade malignant bone tumors. Stage 3 enchondromas, and borderline and Grade 1 chondrosarcomas usually are located centrally in the medullary canal of long bones. There is only minimal involvement of the endosteal lining of the cortex, although treatment with curettage and cryosurgery will leave a stable situation, comparable with the experimental setup of the current study. Usefulness of bone grafting under these circumstances is questionable, given the results of the current study. Giant cell tumors of bone usually are located at the epiphyseal and metaphyseal site of long bones and show destruction of the cortical lining with disruption of the mechanical integrity. Curettage, adjuvant cryosurgery, and reconstruction will result in a construct that may provide cyclic loading of a bone graft, so incorporation might be successful in these cases.

The usefulness of bone grafts in cryosurgical treatment of bone tumors is debatable. Cryosurgery attenuates the host bed of the graft and therefore may prohibit graft incorporation in theory. However, the current study showed revascularization of the graft despite cryosurgical treatment, but this was followed by resorption and failed incorporation. Bone grafting did not contribute to a faster recovery of torsional strength. The mechanical characteristics of the defect may be important for incorporation of bone grafts. Additional animal experiments, using other models, are necessary to evaluate the incorporation process in relation to different type of defects. In the future a more rational application of bone grafts in the cryosurgical treatment of bone tumors can be achieved.

ACKNOWLEDGMENTS

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Chapter 8

FIBROUS DYSPLASIA OF BONE; MANAGEMENT AND OUTCOME OF 20 CASES

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ABSTRACT

Fibrous dysplasia of bone is difficult to manage because of its variable clinical course with many different methods of treatment reported. Therefore we report on our experience. We reviewed a series of 20 patients with 32 lesions included. The average age at the time of diagnosis was 32 years for monostotic disease, 26 years for polyostotic disease and 3 years for McCune-Albright syndrome. The median follow-up period was 6 years. Functional and radiographic outcomes were scored. Monostotic disease mostly presented with a circumscribed lesion and monitoring was often sufficient. Symptomatic circumscribed lesions showed satisfactory outcome when treated with curettage, cryosurgery and bone grafting. Lesions of the extended type were most of all seen in polyostotic disease and eventually needed operative treatment. In case of bony deformity corrective osteotomies and rigid internal fixation were performed in addition to curettage, cryosurgery and bone grafting. In polyostotic disease expected outcomes were good, but in McCune-Albright syndrome, results were uniformly poor.

INTRODUCTION

Fibrous dysplasia of bone is characterized by immature fibrous connective tissue and poorly formed immature trabecular bone[8]. Fibrous dysplasia can compromise the structural integrity of affected bones leading to recurrent fractures and skeletal deformities. Activating mutation within the Gs gene have been described in bone cells of patients with fibrous dysplasia, and in various other tissues of patients with the McCune-Albright syndrome[2,5,20,28]. This results in increased activity of the Gs protein and increased cAMP formation. Excess cAMP probably effects normal maturation of precursor osteogenic cells to normal osteoblast cells[19]. Somatic mutation of this gene early in embryogenesis could result in the mosaic population of normal and mutant-bearing tissues that may underlie the clinical manifestations of this disease.

The clinical picture of fibrous dysplasia is diverse. Its manifestation can be monostotic, polyostotic or polyostotic in combination with skin pigmentation and dysfunction of the endocrine system (McCune-Albright syndrome)[1]. Various treatments are reported depending on age at the time of diagnosis, type and location of the lesion and range from curettage with bone grafting to massive cortical bone grafting, particular in lesions of the femoral neck and to intramedullary fixation in extended lesions with deformity[9,12,13,26]. The intent of operative treatment of the extended lesions is not eradication of the lesion but the correction or prevention of bony deformities.

Both the diversity of the disease and the multiple treatment modalities make fibrous dysplasia difficult to manage. Therefore we reviewed 20 patients and report on our experience with fibrous dysplasia in terms of treatment, tumor control and functional outcome.

MATERIALS AND METHODS

A retrospective study was performed in 20 patients with histologically confirmed fibrous dysplasia who visited our clinic between 1992 and 1998. Thirteen patients had monostotic disease, four polyostotic disease and three McCune-Albright syndrome. In case of polyostotic

Table 8-I

Clinical data of the group of 20 patients with fibrous dysplasia

Patient number	Type of FD	Type of lesion	Gender	Age at the time of diagnosis (years)	Follow-up period (months)	Primary complaints	Lesions included	Site	Comments
1	M	C	F	22	24	pain	femoral neck	L	-
2	M	C	M	22	24	found by chance	femoral diaphysis	L	-
3	M	C	M	27	68	swelling	rib	R	-
4	M	C	M	59	77	pain	proximal femoral diaphysis	L	-
5	M	E	M	45	403	pain	femoral neck	L	-
6	M	C	M	48	29	found by chance	rib	L	-
7	M	C	M	33	25	pain	distal humerus	L	-
8	M	C	M	35	46	found by chance	proximal humerus	R	-
9	M	C	M	13	70	pain	femoral neck	R	-
10	M	C	F	39	24	found by chance	femur (intertrochanteric)	L	-
11	M	C	F	30	43	pain	femoral neck	R	secondary ABC
12	M	E	M	26	399	fracture	fibula	R	-
13	M	E	F	12	144	fracture	humerus	L	-
14	P	E	M	47	26	fracture	humerus	R	endocrine abnormalities
15a	P	C	M	5	287	-	femoral diaphysis	L	-
15b		E		5	287	fracture	femoral diaphysis	R	-
15c		C		5	287	-	tibial diaphysis	L	-
16a	P	E	F	33	360	pain	total femoral involvement	L	-
16b		E		33	360	-	proximal tibia	L	-
17a	P	E	F	18	259	pain	femoral neck	R	-
17b		E		18	259	-	proximal tibia	R	secondary ABC
17c		C		18	259	-	distal humerus	R	-
18a	MA	E	M	2	209	-	total femoral involvement	L	Wilms' tumor (bilateral)
18b		E		2	209	fracture	total femoral involvement	R	-
18c		E		2	209	-	total tibial involvement	L	-
18d		E		2	209	-	total tibial involvement	R	-
19a	MA	E	M	6	156	fracture	proximal femur	L	-
19b		E		6	156	-	femoral neck and diaphysis	R	-
20a	MA	E	M	2	288	fracture	total femoral involvement	L	renal rickets
20b		E		2	288	-	total femoral involvement	R	-
20c		E		2	288	-	total tibial involvement	L	-
20d		E		2	288	-	total humeral involvement	R	-

FD= fibrous dysplasia; M= monostotic; P= polyostotic; MA= McCune-Albright syndrome; C= circumscribed lesion[3]; E= extended lesion[3]; ABC= aneurysmal bone cyst.

Table 8-II
Details on treatment of the group of 20 patients with fibrous dysplasia

Patient nr.	Latest treatment	Prior treatments	Prior treatments	Radiographic results	Functional results
1	CUR + CRYO + FG + BCG [22]			S	S
2	no treatment			S	S
3	no treatment			S	S
4	no treatment			S	S
5	CUR + CRYO + FG + BCG [45]	CUR + BCG [33]	CUR + BCG [33]	U	S
6	no treatment			S	S
7	CUR + CRYO + BCG [33]			S	S
8	CUR + CRYO + BCG [35]			S	S
9	CUR + CRYO + BCG [13]			U	S
10	no treatment			S	S
11	CUR + CRYO + BCG [30]			S	S
12	marginal excision [26]	CUR [4]		S	U
13	CUR + CRYO + BCG [12]			U	S
14	CUR + CRYO + BCG [47]	sling (#) [47]		S	S
15a	cast (#) [14]			S	S
15b	PF (# diaphysis) [11]	cast (#) [9]	NF (#) [8 and 5]	S	S
15c	no treatment			S	-
16a	CUR + megaprosthesis knee[60]	SCO [47]	ITO [33]	S	S
16b	CUR + megaprosthesis knee [60]			S	-
17a	CUR + BCG + PF [18]			S	-
17b	CUR + CRYO + FG + BCG [35]			S	S
17c	CUR + BCG [27]			S	S
18a	CUR diaphysis + CRYO + FG + BCG [16]	O + NF [12]	cast (#) [14, 13, 7 and 4]	U	U
18b	CUR + CRYO + O + FG + BCG + NF [16]	SCO [10]	SO [9 and 6], etc.	U	U
18c	CUR + CRYO + O + FG + BCG + NF [16]	O [12]	SO [10], etc.	S	-
18d	CUR + SO + BCG + NF [16]	SO [10]	cast (#) [9]	U	-
19a	marginal excision + hemi-arthroplasty [15]	ITO [8]	ITO (#) [5]	S	U
19b	CUR + CRYO + FG + BCG + NF [15]			S	S
20a	SO + FG + NF [13]	ITO [6]	cast (#) [9, 7, 2 and 2]	U	U
20b	cast (# diaphysis) [15]	cast (#) [7]	ITO [6]	U	U
20c	SO + NF [11]	cast (#) [9, 8 and 8]		U	-
20d	cast (# diaphysis) [20]			U	U

CUR=curettage; CRYO=cryosurgery; FG=fibula graft; BCG=bone chip graft; [ ]=age at the time of treatment (yr); #=fracture; PF=plate fixation; NF=nail fixation; SCO=supracondylar osteotomy; ITO=intertrochanteric osteotomy; O=osteotomy; SO=Sofield osteotomy (multiple level corrective osteotomy with intramedullary nail fixation)[25].

fibrous dysplasia only symptomatic lesions of clinical significance were taken in account, though 32 lesions in 20 patients were included. There were 14 men and 6 women. The median follow-up period was 6 years (2-34). The mean age at the time of diagnosis was 32 years (12-59) for monostotic disease, 26 years (5-47) for polyostotic disease, and 3 years (2-6) for McCune-Albright syndrome. A bilateral Wilm's tumor occurred in patient number 18 with McCune-Albright syndrome. Further details on primary complaints, affected bones and medical history are listed in Table 8-I. Fibrous lesions were operated upon if they showed a progressive deformity or an impending fracture.

Of the 32 lesions included in these series 8 lesions were treated non-operatively. In polyostotic disease and McCune-Albright syndrome multiple lesions were managed non-operatively, but these were not included because of clinical insignificance. A total of 37 pathological fractures

Figure 8-1. Anteroposterior (A) and Lateral (B) radiograph of the left distal humerus in Patient 7 show an osteolytic expansile lesion with a ground-glass appearance. This image is characteristic for circumscribed type of fibrous dysplasia. The MR images, T1 weighted, sagital pre- (C) and post (D) gadolinium administration show the enhancement of the dysplasia and the endosteal irregularities (arrow). After curettage, adjuvant cryosurgery, and bone grafting, the postoperative radiographs (E,F) show the graft that 17 months postoperatively (G,H) is progressively incorporated in the bony structures.

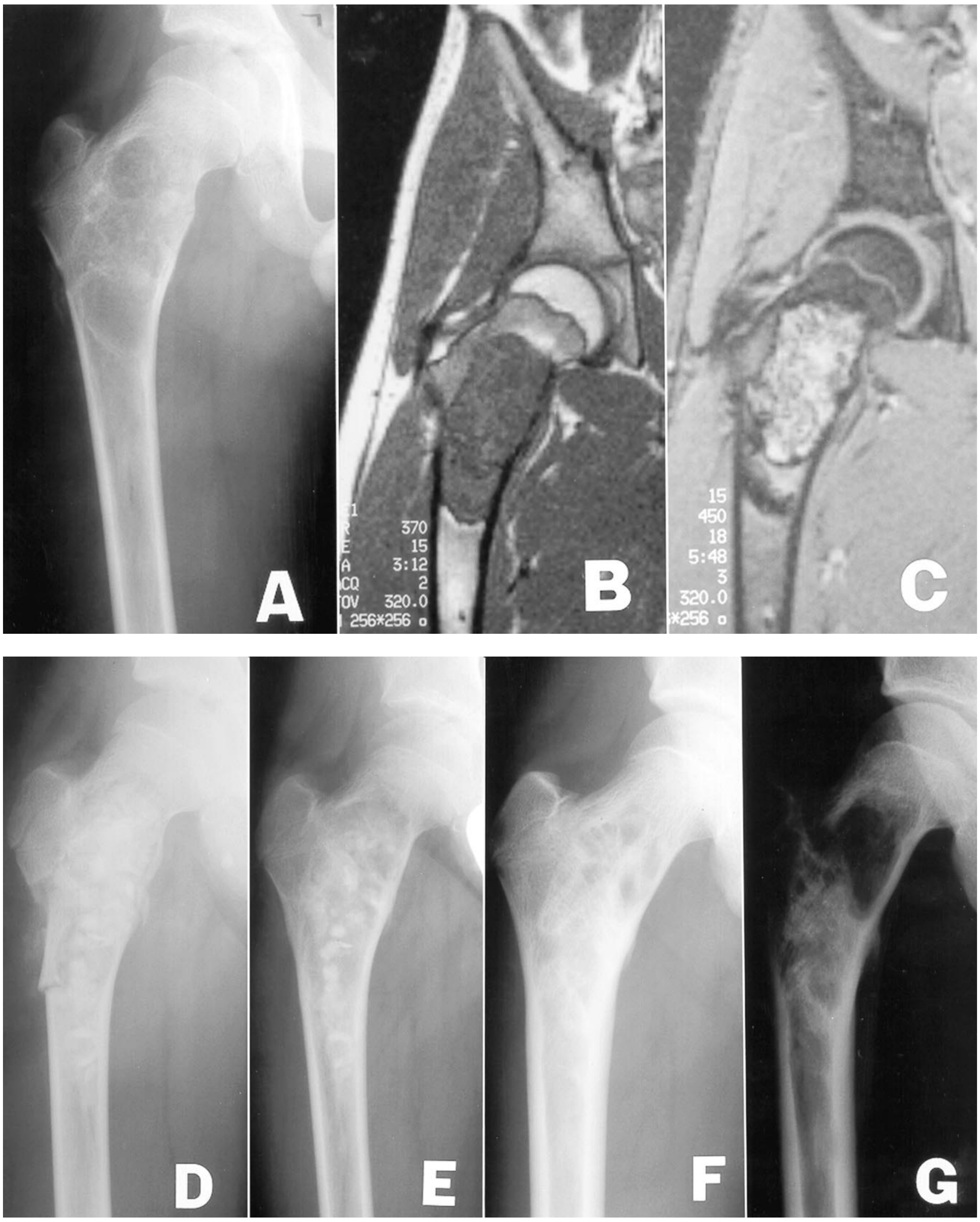

Figure 8-2. Anteroposterior radiograph (A) of a circumscribed lesion of the right hip in Patient 9 after biopsy. Less than one-fourth of the entire femur and only the medial cortex are involved. The coronal MR images before biopsy, T1 weighted (B) and T2 weighted, fast spin echo sequence (C) show an inhomogeneous lesion without clear expansion. The postoperative follow-up is shown in figures D (0 month), E (6 months), F (24 months) and G (60 months). There is a gradual resorption of the bone graft but with a recurrence of the fibrous dysplasia in the femoral neck. So far, the patient is asymptomatic and no treatment is planned.

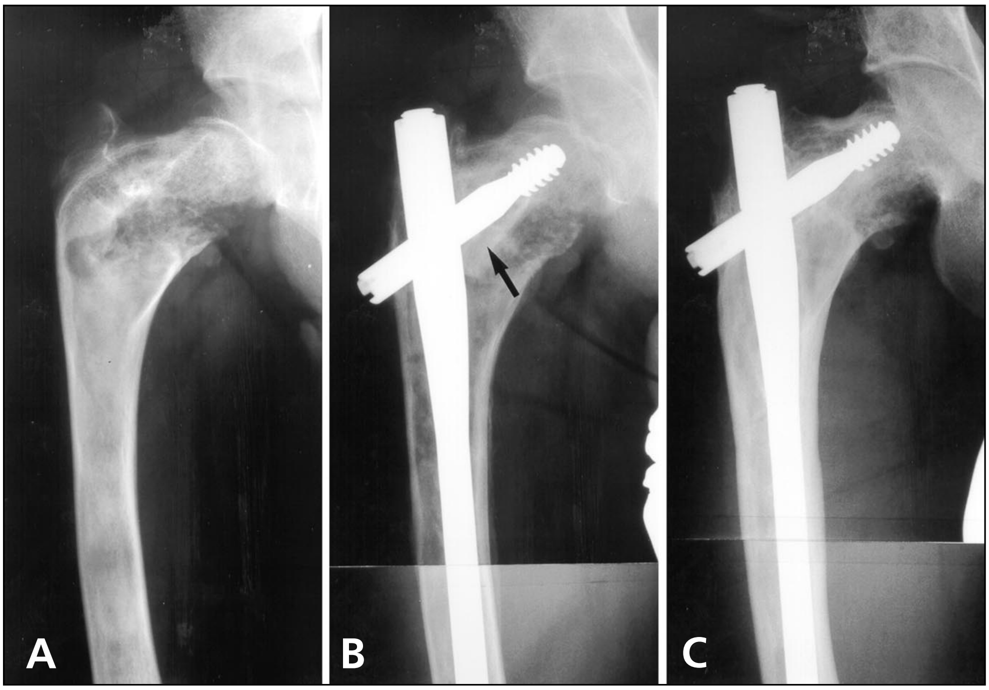

Figure 8-3. Anteroposterior radiograph (A) of an extended lesion of the right proximal femur in Patient 19. There is involvement of more than one-fourth of the entire femur and both cortices with a slight varus deformity. An osteolytic lesion of the femoral neck and multiple endosteal erosions are present. The postoperative follow-up is shown in figures B (10 weeks) and C (3 years). After curettage, cryosurgery, and bone grafting the lesion is augmented with an intramedullary nail and a massive fibular allograft (arrow). Improvement of the bone stock during follow-up.

occurred in 12 lesions during the follow-up period. All fractures were treated conservatively and no pseudarthrosis was noted. Various surgical techniques were used depending on type, location and activity of the lesion (Table 8-II). Symptomatic lesions were treated with curettage and bone grafting. Since 1992 cryosurgery was applied as a local adjuvant, using a liquid nitrogen spray (ERBOKRYO NL, ERBE, Nieuwegein, The Netherlands)[21]. In lesions with insufficient bone stock massive cortical allografts and internal fixation were supplemented. Corrective osteotomies with intramedullary fixation were performed in case of bony deformities.

Postoperatively, patients were allowed to exercise with limited weight bearing for about three months, regardless of the use of internal fixation.

For evaluating the outcome the functional evaluation system of the Musculoskeletal Tumor Society was used[10]. A numerical score and percentage rate was calculated for the diseased extremity. A percentage of 70% or less was considered as an unsatisfactory result[10].

Lesions were classified on radiographs as *circumscribed* or *extended* according to Andrisano's criteria[3]. Circumscribed lesions (Figure 8-1) involve less than one-fourth of the entire bone segment and only one cortex. All other lesions are extended.

When evaluating the radiographic result at follow-up examination attention was paid to progression of the lesion or local recurrence, a pathological fracture and a progressive deformity. With one or more of these items present the radiographic result was considered as unsatisfactory.

RESULTS

Monostotic disease

Five out of 13 patients with monostotic fibrous dysplasia had no complaints and since their lesions did not compromise the structural integrity of the bone they were not further treated.
Three patients (number 5, 12, and 13) had an extended lesion. A progressive lesion of the femoral neck in Patient 5 was eventually treated with curettage, adjuvant cryosurgery and bone grafting (bone chips with massive allograft) after two prior surgical procedures. Because of a localized recurrence of the lesion in the femoral neck at 5 years follow-up the radiographic result was unsatisfactory. In Patient 12 the lesion of the proximal fibula was eventually eradicated with a marginal excision. In Patient 13 an extended lesion of the humerus was treated with curettage, adjuvant cryosurgery and bone grafting. The radiographic result was unsatisfactory due to a pathological fracture 3 years postoperatively.
Five patients had a symptomatic circumscribed lesion that was treated by curettage, adjuvant cryosurgery, and bone grafting (Figure 8-1). Except for Patient 9 the radiographic results were satisfactory (Figure 8-2). Progression of a circumscribed lesion to an extended lesion was never seen in monostotic disease.
Twelve out of 13 patients with monostotic disease showed a satisfactory functional result at follow-up examination. Patient 12 was scored as unsatisfactory because of a MSTS FE score of 70% after marginal excision of the extended lesion; he suffered from modest pain, recreational restrictions, a limited walking ability, and a moderate emotional acceptance.

Polyostotic disease

Four patients had polyostotic fibrous dysplasia with in total nine lesions of clinical significance. Curettage and bone grafting with or without adjuvant cryosurgery was performed in three lesions. In two lesions loss of bone stock necessitated additional rigid internal fixation and in one patient two adjacent periarticular lesions were treated with a megaprosthesis. Two lesions were not treated operatively.
Three out of nine lesions were of the circumscribed type. Two circumscribed lesions were just monitored and one was treated with curettage and bone grafting. The six extended lesions needed operative treatment in all cases, sometimes with multiple procedures to deal with a recurrent fracture and deformity. All the lesions in polyostotic disease had a satisfactory radiographic result. All the patients with polyostotic fibrous dysplasia showed a satisfactory functional outcome.

McCune-Albright syndrome

Three patients with 10 extended lesions of clinical significance were diagnosed as McCune-Albright syndrome. Symptoms presented at the age of 2 to 6 years. All patients were repeatedly treated with corrective osteotomies and intramedullary fixation for the management of aggressive progression of the disease throughout the follow-up period. In Patient 18 an attempt was made to correct the shepherd crook deformity; the procedure was aborted because of massive blood loss during exposure of the proximal femur. Patient 18 and 20 were treated with bisphosphonates in an attempt to modify the aggressive behavior of the disease. No response could be observed.
Seven lesions demonstrated progress of the deformity and an unsatisfactory radiographic result at the time of follow-up. Patient 18 and 20 developed a sheperd crook deformity of the bilateral

Table 8-III

Details of studies on fibrous dysplasia

Author	Type of FD	No. of patients	Age (years)	Follow-up period (years)	Conservative treatment	Curettage	Curettage + bone graft	Curettage + bone graft + cryosurgery	Cortical bone graft	Internal fixation	Corrective osteotomy	En bloc excision
Stephenson '87	M	43	15	10	12 [5]	1 [0]	23 [13]	-	-	7 [1]	-	3 [0]
	P	-	-	-	48 [25]	-	18 [14]	-	-	16 [2]	-	3 [1]
Döhler '86	M	4	40	8	-	3 [0]	1 [0]	-	-	-	-	-
	P	9	8	10	2 [0]	-	-	-	-	4 [1]	6 [3]	-
Henry '69	M	28	?	12	-	-	24 [9]	-	-	-	-	4 [0]
	P	-	-	-	-	-	-	-	-	-	-	-
Harris '62	M	13	21	16	4 [0]	-	11 [5]	-	-	-	-	9 [1]
	P	37	13	24	-	-	-	-	-	7 [3]	11 [9]	-
Stewart '62	M	16	18	5	1 [1]	2 [1]	12 [1]	-	-	2 [?]	1 [1]	1 [0]
	P	4	9	15	2 [1]	1 [1]	3 [2]	-	-	1 [?]	-	-
Nakashima '84	M	8	21	9	-	-	7 [1]	-	-	-	-	1 [1]
	P	-	-	-	-	-	-	-	-	-	-	-
Andrisano '91	C	37	9	7	-	38 [22]	-	-	-	-	-	2 [1]
	E	28	9	7	-	45 [45]	-	-	-	31 [31]*8 [2]**	-	-
Enneking '86	M	10	18	7	-	-	-	-	10 [2]	-	-	-
	P	23	5	6	-	-	-	-	5 [0]	-	-	-
Guille '98	M	9	9	14	11 [11]	-	9 [5]	-	1 [0]	-	5 [1]	-
	P	8	13	15	21 [13]	-	9 [6]	-	-	1 [1]	16 [11]	-
Keijser	M	13	32	9	5 [0]	-	-	6 [2]	-	-	-	1 [1]
	P	7	16	19	3 [1]	-	1 [0]	5 [2]	-	2 [0]	6 [6]	3 [2]
Total		297			109 [57]	90 [69]	118 [56]	11 [4]	16 [2]	79 [41]	45 [31]	27 [7]

[ ]= number of poor results according to the author's description; *= rigid internal fixation; **= intramedullary nailing; M= monostotic; P= polyostotic; C= circumscribed lesion[3]; E= extended lesion[3].

proximal femur at the time of follow-up examination. In lesion number 18c, 19a, and 19b the radiographic result was satisfactory. The result of lesion 19b is shown in Figure 8-3.
In only two out of 10 lesions (19b and 20d) the functional outcome was satisfactory.

DISCUSSION

The first symptoms of fibrous dysplasia are usually noted between 5 and 20 years of age; the more extended the disease the earlier the onset of symptoms[4]. It is believed that fibrous dysplasia loses it's potential to proliferate at the end of growth of the patient and matures into fibro-osseous tissue[3,4,7,9,11,27]. In our series, however, 13 patients presented after the age of 20 years.
The importance of age at the time of diagnosis regarding treatment has been emphasized[8]. Those lesions that showed an impending fracture or a progressive deformity were operated upon in these series, regardless of age. All the other lesions were managed non-operatively. In general, lesions that presented at an early age were biologically aggressive leading to bony deformities that needed surgical treatment.
Nonsurgical treatment with bisphosphonates is an option for those patients with generalized skeletal involvement. Preliminary studies report relieve of pain and regression of fibrous lesions with intravenous infusions of pamidronate[6,16]. In our series two patients with McCune-Albright syndrome have been treated with bisphosphonates without a beneficial effect on the course of the disease.

In these series, **monostotic fibrous dysplasia** was usually associated with circumscribed type lesions and when this was the case, the fibrous dysplasia was minimally aggressive, lesions did not give rise to bony deformities, and monitoring was often sufficient. When operative treatment is performed, a single procedure of curettage, cryosurgery, and bone grafting without additional internal fixation is sufficient. A satisfactory functional outcome is the rule; we encountered three local recurrences on radiographic examination in lesions that were all of the extended type.
In contrast to our experience, studies on curettage and bone grafting of *monostotic* fibrous dysplasia, report negative results attributed to incomplete removal of the fibrous tissue and subsequent replacement of the graft by dysplastic bone (Table 8-III)[3,9,12,14]. Whether or not these lesions are of the circumscribed type is not specified. The benefit of adjuvant cryosurgery in the treatment of monostotic fibrous dysplasia remains the question for we did not perform a controlled trial. We apply cryosurgery as local adjuvant therapy to intralesional resection because of its favorable results in reduction of the local recurrence rate of benign and low-grade malignant bone tumors[15,17,18,22-24].

Polyostotic fibrous dysplasia presented most commonly with extended lesions, while lesions in **McCune-Albright syndrome** were all of the extended type. Marked progression of the disease is seen in those cases that presented before the age of 10 years, supporting the relation between age of onset and biological aggressiveness[14]. Most extended lesions in *polyostotic* disease sustained multiple pathological fractures and multiple operative procedures focused on prevention or correction of bony deformities. Both functional outcome and radiographic result show favorable results in extended lesions in polyostotic disease. Extended lesions in *McCune-*

Albright syndrome tend to progress despite all efforts, however, including the local adjuvant cryosurgery, resulting in poor functional and radiographic outcome.
Concerning the treatment of progressive extended lesions in polyostotic disease, there is agreement about the disappointing results of curettage and bone grafting. The early treatment with corrective osteotomies and rigid internal fixation to prevent bony deformities is emphasized[3,4,12,26]. Enneking suggested the use of massive cortical allografts to supplement dysplastic bone on condition that an existing deformity is corrected and internally fixated[8]. Studies on fibrous dysplasia report variable expected outcomes in polyostotic disease probably due to the diversity of the patient groups (Table 8-III). Such a marked difference in expected outcome as we found between polyostotic fibrous dysplasia and McCune-Albright syndrome has not been demonstrated before.

CONCLUSIONS

It is our experience, in contrast to earlier reports, that fibrous dysplasia usually presents after the age of 20 years. Circumscribed lesions of fibrous dysplasia, most of them part of monostotic disease, are not likely to progress. When complaints arise, operative treatment with curettage, cryosurgery, and bone grafting shows a satisfactory outcome. Extended lesions may result in bony deficiency or deformities necessitating additional internal fixation, massive allografts, or corrective osteotomies. In our series, functional outcomes of extended lesions in monostotic and polyostotic disease are satisfactory, although some lesions need multiple operative procedures. On the other hand, extended lesions in McCune-Albright syndrome result in poor clinical outcomes. We continue the use of cryosurgery in the treatment of fibrous dysplasia because of its favorable results, though this can not be stated by controlled studies.

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Chapter 9

ONCOLOGIC AND FUNCTIONAL RESULTS AFTER TREATMENT OF GIANT CELL TUMORS OF BONE

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ABSTRACT

Surgical treatment of giant cell tumor of bone has always been a difficult problem, because of its local aggressive behavior. In a retrospective study of 36 patients, with various surgical treatments, we report on the oncologic and functional outcome. The average age at the time of diagnosis was 34 years, and the median follow-up period was 7 years. Twenty-three patients were treated by intralesional, and 11 patients by extralesional excision. Two patients received radiotherapy only. Oncologic and functional outcome were scored. Intralesional excision resulted in satisfactory functional results, but 7 local recurrences (30%) were encountered. After extralesional excision (marginal or wide) no local recurrences were noticed. Wide excision was associated with poor functional outcome, while marginal excision showed good functional results. For the treatment of giant cell tumor of bone, intralesional excision with a local adjuvant is recommended, because of good functional outcome with acceptable local tumor control.

INTRODUCTION

Giant cell tumor of bone (GCT) is notorious for its local aggressive behavior and the tendency to recur after intralesional operative treatment. Many reports are published since GCT was given its name by Bloodgood in 1912[5]. GCT is an uncommon bone tumor, representing almost 5% of all primary bone tumors. Today, GCT is considered a benign locally aggressive lesion, although 3% is primarily malignant[11,27] or will undergo malignant changes, may metastasize following radiation therapy[6,33] or after several local recurrences[17,39]. For this reason, treatment of GCT has always been a challenging problem. A wide variety of procedures has been used for treatment of GCT, such as intralesional procedures (curettage) with or without the use of local adjuvants, extralesional procedures (marginal and wide excisions), and radiotherapy. Extralesional procedures will usually eradicate the disease, but result in discontinuity of the bone, for which a reconstructive procedure is necessary. This reconstruction may coincide with high morbidity and probably leads to functional restrictions in the patient. Intralesional excision, with the use of local adjuvants, might give better functional outcome, but at greater risk of local tumor recurrence, when compared to extralesional excisions. To compare extralesional with intralesional procedures, we performed a retrospective study covering 36 patients who have been treated for GCT according to various techniques. Management and functional outcome are reported with special reference to the role of cryosurgery as local adjuvant.

MATERIALS AND METHODS

Thirty-six patients, with histologically proven GCT and a follow-up of at least 2 years, were included in this retrospective study. There were 19 male and 17 female patients. The average age at the time of diagnosis was 34 years (10-63). The time of follow-up ranged between 2 and 31 years with a median follow-up period of 7 years. Seven patients were referred to our clinic after treatment elsewhere because of persistence of tumor in four patients (number 2, 23, 25, and 28)

Table 9-I
Details of the present 36 patients with giant cell tumor of bone

Patient number	Sex / Age at the time of diagnosis (yr)	Follow-up period (yr)	Primary complaints	Localisation	Stage	Prior treatment elswhere
1	M/21	31	Pain	Femoral Neck	2	-
2	F/32	5	Pain	Proximal Tibia	2	IE + HBG
3	M/28	17	Pain	Proximal Fibula	2	-
4	F/34	17	Fracture	Medial Femoral Cond.	2	-
5	M/52	10	Fracture	Lateral Femoral Cond.	2	-
6	F/24	11	Pain	Distal Tibia	3	-
7	M/39	3	Pain	Proximal Femur	3	-
8	F/25	4	Pain	Proximal Humerus	3	-
9	F/21	8	Pain	Distal Ulna	3	-
10	F/23	3	Pain	Distal Radius	3	-
11	F/26	4	Fracture	Distal Femur	3	-
12	M/42	12	Pain	Distal Humerus	3	-
13	M/10	12	Pain	Proximal Tibia	3	-
14	F/41	5	Pain	Proximal Fibula	3	-
15	M/29	3	Pain	Distal Femur	3	-
16	F/53	3	Pain	Medial Femoral Cond.	3	-
17	M/34	4	Pain	Distal Radius	3	-
18	F/26	2	Fracture	Lateral Femoral Cond	3	Two times IE + Phenol
19	F/36	2	Fracture	Lateral Femoral Cond.	3	-
20	F/17	9	Fracture	Lateral Femoral Cond.	3	IE + ABG
21	M/63	4	Pain	Lateral Femoral Cond.	2	-
22	M/29	5	Pain	Lateral Femoral Cond.	3	-
23	M/50	3	Pain	Sacrum (S1+S2)	3	RT
24	F/31	6	Pain	Sacrum (S4+S5)	3	-
25	M/29	6	Pain	Lamina TH 4	3	IE Lamina TH 3-5
26	M/27	2	Pain	Proximal Fibula	2	-
27	F/25	14	Pain	Distal Radius	3	-
28	M/27	22	Fracture	Lateral Femoral Cond.	3	Meniscectomy
29	F/39	5	Fracture	Proximal Humerus	3	-
30	M/43	20	Fracture	Proximal Humerus	3	-
31	M/51	18	Pain	Medial Femoral Cond.	3	-
32	M/39	12	Pain	Lateral Femoral Cond.	3	-
33	M/31	20	Fracture	Proximal Humerus	3	-
34	M/34	21	Fracture	Proximal Humerus	3	-
35	F/19	27	Swelling	Os Capitatum	2	-
36	F/21	14	Pain	Distal Tibia	3	ME + RT (8Gy)

M= male; F= female; Cond.= condyle; IE= intralesional excision; RT= radiotherapy; Gy= gray; ABG= autologous bone grafting; HBG= homologous bone grafting; TH= thoracal; ME= marginal excision.

and local recurrence in three patients (number 18, 20, and 36). At the time of admission, 24 patients (67%) experienced pain, 11 patients (30%) had a fracture and one patient (3%) noticed a swelling. All tumors were staged according to the System for the Staging of Muskuloskeletal Tumors of Enneking[12]. Twenty-eight GCTs were classified aggressive (stage 3) and eight were classified active (stage 2). The details of all 36 patients are shown in Table 9-I.

Intralesional excision (curettage)

Twenty-three patients were treated by intralesional excision (curettage). In two patients no adjuvant therapy was used. In four patients the defect was filled with cement as adjuvant therapy and for the purpose of reconstruction. Seventeen patients received cryosurgery after curettage. Three cycles of cryosurgery were performed to extend the surgical margin, utilizing a liquid nitrogen spray[37]. To monitor the cryosurgery for efficiency and unwarranted morbidity, thermocouples were placed in and around the lesion[35]. An exception to the surgical procedure as described above is Patient 13, who has been treated in 1980. Here, the “direct pour technique” of cryosurgery as described by Marcove et al.[21] was used. After curettage, the remaining defects were filled with allo- or autograft bone chips, cement or hydroxyl apatite crystals. If the strength of weight bearing bones was compromised by the lesion and the surgical procedure, internal fixation was performed preferably using a titanium plate and screws, because of magnetic resonance compatibility.

Extralesional excision

Eleven patients were treated by an extralesional procedure, four patients by a marginal excision and seven patients by a wide excision. For reconstruction an endoprosthesis or arthrodesis was used. Two patients did not undergo a surgical procedure, and were treated by radiotherapy only. Details of the treatment are shown in Table 9-II.

At the time of follow-up, all patients were examined and scored according to the System for the Functional Evaluation of Surgical Management of Muskuloskeletal Tumors of Enneking[13]. A routine radiographic examination was performed, augmented by bone scintigraphy and magnetic resonance imaging (MRI) when indicated.

RESULTS

Intralesional excision (curettage)

Seven out of the 23 patients (30%) who were treated by curettage developed a local recurrence. One soft tissue recurrence was found in Patient 4, eight years after curettage, in combination with cement as local adjuvans. She had an intralesional excision and developed a local re-recurrence after 9 years, which was treated by cryosurgery. The six other local recurrences of bone were found between 4 and 28 months after intralesional excision with cryosurgery. Four patients were treated by cryosurgery again. Ever since, Patient 12 has been free of relapse. Patient 10 was successfully treated by cryosurgery for the third time, while Patient 17 had a marginal excision of the distal radius followed by allograft reconstruction and Patient 22 had a marginal excision of a soft tissue recurrence. Patient 13 was subsequently treated by an amputation at persistent specific request of the family and Patient 9 underwent a wide excision of the ulna.

Postoperatively, one deep wound infection and one case of chronic osteomyelitis were observed. Patient 10 had a transient palsy of the superficial radial nerve and Patient 14 had a transient palsy of the peroneal nerve. One patient (number 25) with a sacral GCT had a permanent nerve palsy, resulting in incontinence for faeces.

The average functional score of all patients initially treated by intralesional excision (Patients 1 to 23) was 89% (47-100). If we consider the patients who have been treated exclusively by intralesional excision, the average score increases to 92% (53-100). Figure 9-1 shows the radiographs of the intralesional procedure in Patient 11.

Table 9-II

Treatment and functional outcome of the present series of 36 patients with giant cell tumor of bone

Patient number	Key treatment	1th Local recurrence / Subsequent treatment	2nd Local recurrence / Subsequent treatment	Postoperative complications/ Subsequent treatment	Status	MSTS FE score (%)
1	CUR+ABG	-	-	-	CDF	93
2	CUR+PMMA	-	-	-	NED	80
3	CUR	-	-	-	CDF	100
4	CUR+PMMA	STR / IE	LR / CUR+CRYO	DWI / Necrotectomy	AWD	53
5	CUR+PMMA	-	-	-	CDF	100
6	CUR+PMMA	-	-	-	CDF	100
7	CUR+CRYO+K-nail	-	-	-	CDF	100
8	CUR+CRYO+HBG	-	-	-	NED	100
9	CUR+CRYO+HBG	LR / WE	-	-	NED	70
10	CUR+CRYO+HBG	LR / CUR+CRYO+HBG	LR / CUR+CRYO+HBG	TNP	NED	100
11	CUR+CRYO+PMMA+HBG+PF	-		-	CDF	100
12	CUR+CRYO+HA	LR / CUR+CRYO+HA		-	CDF	87
13	CUR+CRYO+PMMA	LR / Wide amputation	-	-	CDF	47
14	CUR+CRYO+HBG	-	-	TNP	CDF	100
15	CUR+CRYO+HBG	-	-	-	CDF	100
16	CUR+CRYO+PMMA+PF	-	-	-	CDF	100
17	CUR+CRYO+HBG	LR / CUR+CRYO+HBG	LR / ME	-	CDF	87
18	CUR+CRYO+PMMA+PF	-	-	-	NED	87
19	CUR+CRYO+PMMA+PF	-	-	-	CDF	100
20	CUR+CRYO+HA	-	-	-	NED	80
21	CUR+CRYO+HBG	-	-	-	NED	100
22	CUR+CRYO+HBG	LR / CUR+CRYO+PMMA	STR / ME	-	CDF	100
23	CUR+CRYO+HBG	-	-	COM+PNP / Debridement+GB	CDF	70
24	ME	-	-	-	CDF	100
25	ME+RT (46Gy)	-	-	-PNP, Paraplegic	CDF	n.f.e.
26	ME	-	-	-	CDF	100
27	ME+Arthrodesis	-	-	-	CDF	80
28	Wide amputation	PM / WE	-	-	NED	00
29	WE+Endoprosthesis	-	-	-	CDF	67
30	WE+Endoprosthesis	-	-	COM / Debridement+GB	CDF	60
31	WE+Endoprosthesis	-	-	Loosening 2 times / Amputation	CDF	50
32	WE+Arthrodesis	-	-	-	CDF	60
33	WE+Endoprosthesis	-	-	Fracture prosthesis / Revision	CDF	60
34	WE+Endoprosthesis	-	-	Loosening prosthesis / Revision	NED	70
35	RT (20Gy)	-	-	-	CDF	100
36	RT (30Gy)	-	-	COM / Debridement+GB	NED	70

CUR= curettage; IE= intralesional excision; ME= marginal excision; WE= wide excision; RT= radiotherapy; PMMA= polymethylmethacrylate; CRYO= cryosurgery; ABG= autologous bone grafting; HBG= homologous bone grafting; PF= plate fixation; HA= hydroxyl apatite; LR= local recurrence; STR= soft tissue recurrence; PM= pulmonary metastases; DWI= deep wound infection; TNP= transient nerve palsy; PNP= permanent nerve palsy; COM= chronic osteomyelitis; GB= gentamycine beads; CDF= continuous disease free; NED= no evidence of disease; MSTS FE= Muskuloskeletal Tumor Society Functional Evaluation; n.f.e.= no functional evaluation.

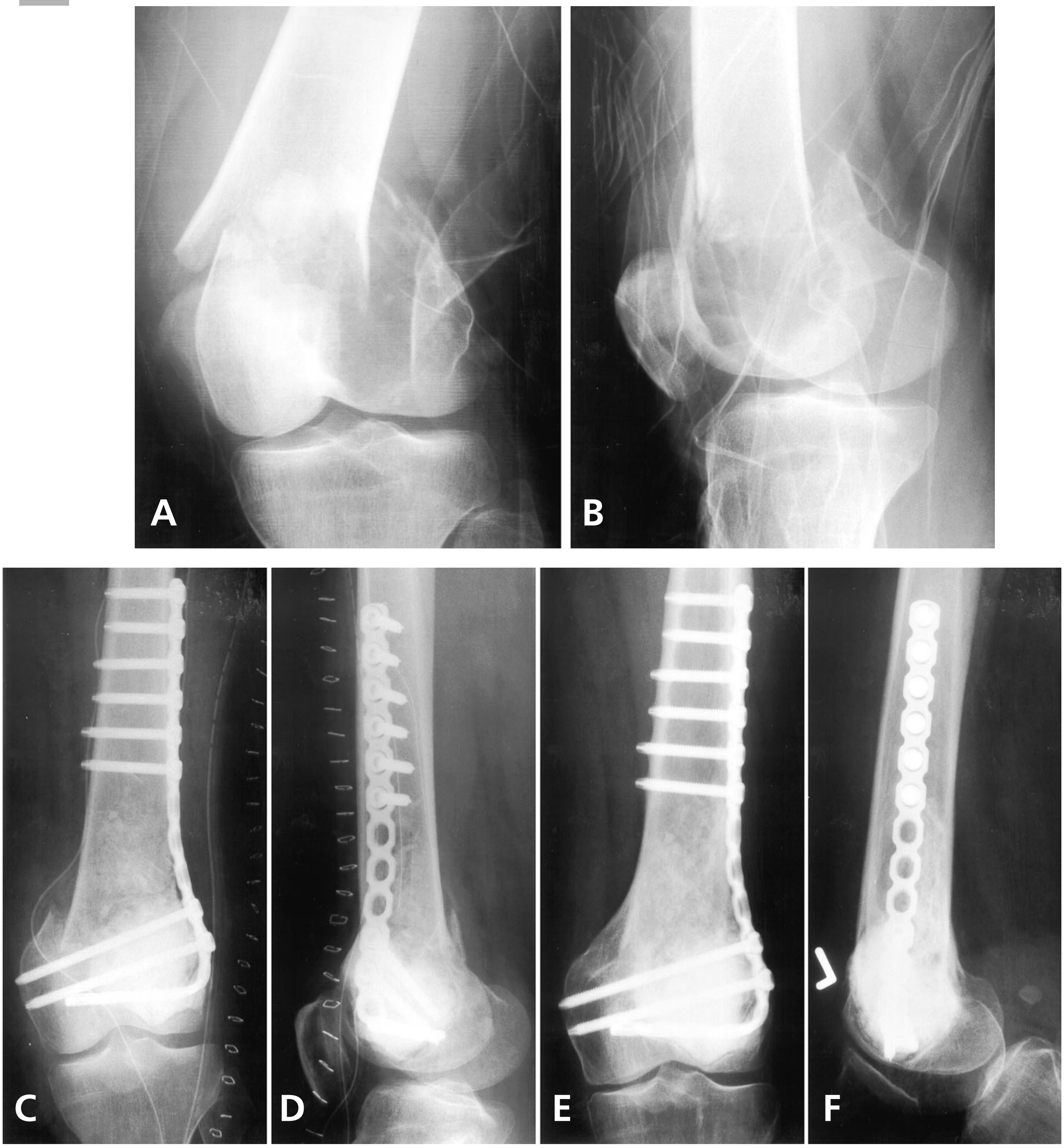

Figure 9-1. Anteroposterior (A) and lateral (B) radiograph of the left distal femur in Patient 11. Extensive osteolytic lesion, involving the epiphysis and metaphysis, with a weakening of the mechanical integrity and subsequent pathological fracture. Postoperative radiographs, anteroposterior (C) and lateral (D) after intralesional excision, cryosurgery, and reconstruction with homologous bone grafting, PMMA, and a titanium alloy plate. Anteroposterior (E) and lateral (F) radiographs 4 years postoperatively. No signs of osteoarthritis or local tumor recurrence are noticed.

Figure 9-2. Anteroposterior (A) and axial (B) radiograph of the right proximal humerus in Patient 29. Osteolytic lesion of the proximal humerus consistent with GCT. Magnetic resonance imaging of the lesion shows a low signal of the intramedullary lesion on the sagital T1 weighed images (C) and an high signal intensity on the T2 weighted images (D), also consistent with GCT. There is destruction of the lateral cortical bone and the dark band-like signal in the lower part of the lesion indicates a (pathological) fracture. Anteroposterior radiograph six years after wide excision with an endoprosthetic reconstruction of the proximal humerus (E) (see next page).

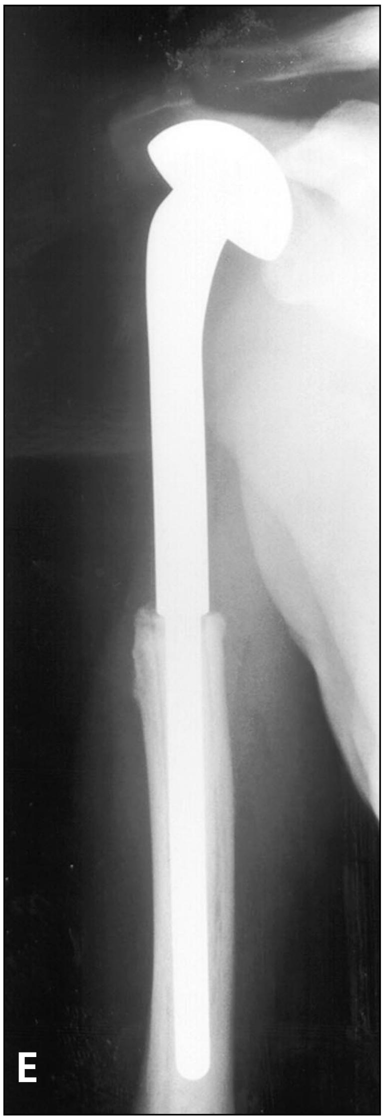

Figure 9-2-E. (See previous page)

Extralesional excision

Four patients underwent a marginal excision of the GCT. No local tumor recurrence was encountered. In one patient (number 27) an arthrodesis was performed to reconstruct the segmental defect. Patient 25 sustained a central spinal cord lesion due to the operative procedure, resulting in paraplegia. Except for this patient, functional outcome was satisfactory after marginal procedures.

In seven patients a wide excision of the GCT was performed. No local recurrences were observed. Eleven years after operation, Patient 28 developed multiple pulmonary metastases, which were successfully treated by wide excision. In five out of seven patients an endoprosthesis was used for reconstruction. Three patients who received an endoprosthesis needed revision because of aseptic loosening or mechanical failure; in one patient this eventually resulted in an amputation. Another patient with an endoprosthesis sustained a deep postoperative infection that had been treated successfully, while retaining the endoprosthesis. Figure 9-2 demonstrates the operative procedure with an endoprosthetic reconstruction in patient number 29, who recovered without complications. Overall functional results of the patients treated by a wide excision were poor.

The two patients treated by radiotherapy showed no local recurrence. Patient 36 developed a chronic osteomyelitis; at 14 years follow-up the functional score was 70%. In Patient 35 the functional score was 100%. Table 9-II shows the details on all treatments, status at the time of follow-up, complications, and functional score.

DISCUSSION

GCT is considered to be a benign, locally aggressive lesion with a high tendency to relapse after intralesional excision. Therefore, many treatments have been advocated to achieve local tumor control. Extralesional excision has been the surgeons' first choice for long time. Although extralesional excisions lead to excellent oncologic results, the functional results are often poor[14,32,40]. Simple curettage, first introduced in 1912 by Bloodgood[5], was associated with a high rate of local recurrence, up to 80%[15], while extralesional excisions resulted in local tumor control in more than 90%[6,14,23]. Therefore, surgeons have been searching for treatments to

preserve the joint function and improve the oncologic outcome at the same time. As a result, local adjuvant therapy was introduced to extend the surgical margin of intralesional excision. Table 9-III presents a review of literature on the treatment of GCTs.
Many different local adjuvants are reported in the literature. *Phenol* is used as a chemical adjuvant after curettage, causing coagulation of all proteins at the surface of the curetted cavity. Recurrence rates are variable (5% to 66%), and phenol is often used in addition to other kinds of adjuvants[8,9,10,14,23,29].
Polymethylmethacrylate (PMMA) is used as thermal adjuvant, though the increase in margin is limited to 1.5 to 2 mm in cancellous, and 0.5 mm in cortical bone[25,31]. PMMA has not often been used as only adjuvant; however, smaller series show excellent functional results with recurrence rates between 0% and 42%[3,29,30,31,41]. Besides the use as thermal adjuvant, PMMA is used for reconstruction in weight bearing bones.
Methotrexate, eluted from PMMA has been reported as a possible effective adjuvant after curettage, but has not yet been investigated in vivo[18].
Radiotherapy is the choice of treatment for GCTs that are technically difficult to operate on, because of its location. Treatment by radiotherapy has always been controversial, because of high recurrence rates[3], and the potential that tumor cells will undergo malignant transformation[6,33]. Recent studies have shown that local control rates of 75% - 85% can be achieved, and the risk of malignant changes is minute[2,7,38].
Cryosurgery for the treatment of localized bone tumors was first introduced by Marcove et al. in 1964, by pouring liquid nitrogen into the curetted cavity[21]. Since then, local recurrence rates between 8% and 57% have been reported for the treatment of GCTs[16,20-22]. According to oncologic principles, the technique of intralesional excision with adjuvant cryosurgery is considered as a marginal procedure[12]. Compared to a marginal procedure, cryosurgery enables preservation of the joint and the supportive function of bone[36,37].

Local recurrence rates after *intralesional excision*, which were observed in our series and compared to those reported in the literature, were relatively high (Table 9-III). Several reasons may account for our local recurrences. Six out of seven local recurrences we observed were classified aggressive (stage 3), although a relationship between histological stage and local recurrence can be questioned[28,34]. GCTs of the distal radius are particularly aggressive and the rate of recurrence seems to be higher[29,41]. Many authors have shown improving results at the end of the learning curve with adjuvant cryosurgery[20,21]. Since we improved our cryosurgical technique by local temperature monitoring, we encountered four local recurrences after initial treatment. Two of them were located in the distal forearm, which remains a difficult location for vigorous freezing, because of the proximity of neurovascular structures.
No fractures, cases of skin necrosis or thrombosis, that are historically attributed to cryosurgery, were observed[16,21,32]. Degenerative changes of the cartilage, known after the application of PMMA, were not observed[3,31]. Functional results after curettage were excellent with an average of 92% and were almost 30% better than those after extralesional excision.

There were no local recurrences in the patients that were treated by *extralesional excision.* We only observed one case of pulmonary metastases. Several large series are reported on the extralesional excision of GCT, involving the joint with excellent local tumor control compared to intralesional procedures with the use of local adjuvants (Table 9-III). Although the oncologic results are good, the disadvantage of extralesional excision was the relatively poor outcome of

Table 9-III

Different types of treatment and local recurrence rates of giant cell tumors of bone

Author	Radiotherapy		IE		IE + burr		IE + cryosurgery		IE +phenol		IE + PMMA		EE	
	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Aboulafia et al[1]	-	-	-	-	-	-	6	1	-	-	-	-	-	-
Bennett et al[2]	16	4	-	-	-	-	-	-	-	-	-	-	-	-
Bini et al[3]	-	-	-	-	-	-	-	-	-	-	38	3	-	-
Blackley et al[4][32]	-	-	-	-	59	7	-	-	-	-	-	-	-	-
Campanacci et al[6]	-	-	151	41	122	10	-	-	-	-	-	-	58	0
Chakravarti et al[7]	7	1	-	-	-	-	-	-	-	-	-	-	-	-
Dahlin et al[8]	-	-	17	4	-	-	-	-	-	-	-	-	6	4
Durr et al[9]-	-	-	-	7	3	-	-	11	1	-	-	11	1	
Gitelis et al[14]	-	-	-	-	-	-	-	-	20	1	-	-	20	0
Goldenberg et al[15]	46	29	136	73	-	-	-	-	-	-	-	-	66	22
Vander Griend et al[41]	-	-	-	-	-	-	-	-	-	-	5	0	18	0
Jacobs et al[16]	-	-	-	-	-	-	12	2	-	-	-	-	-	-
Larsson et al[19]	10	4	30	14	-	-	-	-	-	-	-	-	7	1
Malawer et al[20]	-	-	-	-	-	-	102	8	-	-	-	-	-	-
Marcove et al[21]	-	-	-	-	-	-	52	12	-	-	-	-	-	-
Marcove et al[22]	-	-	-	-	-	-	7	4	-	-	-	-	-	-
McDonald et al[23]	2	-	-	-	-	-	-	-	85	29	-	-	27	2
McGrath[24]	12	6	20	9	-	-	-	-	-	-	-	-	7	0
Mnaymneh et al[26]	6	5	23	13	-	-	-	-	-	-	-	-	21	0
Oda et al[28]	-	-	28	21	6	3	-	-	-	-	-	-	13	0
O'Donnel et al[29]	-	-	-	-	24	4	-	-	11	2	19	8	-	-
Persson and Wouters[30]	2	2	9	3	-	-	-	-	-	-	6	0	5	2
Persson et al[31]	-	-	22	12	-	-	-	-	-	-	14	2	-	-
Schwartz et al[38]	13	2	-	-	-	-	-	-	-	-	-	-	-	-
Sung et al[40]	-	-	-	-	-	-	-	-	52	14	-	-	75	8
Yip et al[42]	-	-	-	-	29	2	-	-	-	-	-	-	15	0
Boons et al	2	0	2	0	-	-	17	6	-	-	4	1	11	0
Total	116	53	438	190	247	39	191	33	179	47	86	14	360	40
Recurrence rate (%)	46		43		16		17		26		16		11	

N= number of patients; R= number of local recurrences; IE= intralesional excision; EE= extralesional excision; PMMA= polymethylmethacrylate.

the functional results, averaging 65%. Patients treated by marginal excision had satisfying functional outcome, except for one patient who sustained a central spinal cord lesion. Functional outcome after wide excision was uniformly poor, and many endoprosthesis related problems were encountered. For obvious reasons, excision and endoprosthetic reconstruction of a functional joint will result in restricted function. Revision surgery will eventually lead to further limitation of the functional result. The average functional score of the patients treated by wide excision was poor (52%).

CONCLUSIONS

Extralesional excision of GCT, involving the joint, gives good local tumor control, but results in poor functional outcome and long-term complications related to endoprosthetic reconstruction. Based on the underlying study, we recommend intralesional excision with adjuvant therapy for the treatment of GCT. Cryosurgery is a powerful local adjuvans, of which the quantity can be monitored and dosed. Given the low complication rate in our series, more vigorous freezing is advised under close local temperature monitoring; Lesions located in the distal radius should be treated with special concern because of its high tendency of local recurrence. Good functional and oncologic outcome can be expected. Marginal excisions are reserved for expandable bones, and wide excisions for malignant GCTs and soft tissue recurrences.

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Chapter 10

SUMMARY, DISCUSSION OF THE AIMS, AND CLOSING REMARKS ON PROSPECTS FOR THE FUTURE

SUMMARY

Cryosurgery is used as a local adjuvant to intralesional excision of active and aggressive benign and low-grade malignant bone tumors. The goal of this additional treatment is to reduce the recurrence rate by freezing remaining tumor cells at the margin of the lesion. Cryosurgery did not become generally accepted in the field of Orthopaedics, despite the promising reports of some pioneers in the late sixties. The widespread application of the cryosurgical technique was probably hampered by rumors about a high complication rate.
Complications of cryosurgical treatment of bone tumors, animal experiments on bone behavior, and clinical outcome after cryosurgical treatment of fibrous dysplasia and giant cell tumor of bone, are highlighted in this thesis.
After a general introduction, the aims of the thesis are presented in **chapter 1**. The following is a summary of the subsequent chapters, concentrating on the aims of the thesis.

AIMS

1. ***To qualify, quantify and discuss the complications related to cryosurgical treatment of bone tumors.***

The study of the effects of freezing and thawing on living cells, that forms a part of cryobiology, is summarized in **chapter 2**. Basic features of the cryosurgical treatment that promotes cell death, are (1) shrinkage of the cell with high concentrations of solutes, (2) intracellular ice formation with disruption of cell organelles and membranes, (3) mechanically induced destruction due to propagation of ice formation, (4) re-crystallization with formation of large ice crystals during thawing, and (5) tissue ischemia due to microcirculatory failure. To induce cell death in cryosurgical practice effectively, consideration should be given to the following technical features: (1) a minimum cooling rate of 50°C/min, (2) a minimum temperature of approximately –50°C at the periphery of the lesion, (3) maintenance of the freeze for a period, (4) a spontaneous and complete thawing period, and (5) repetitive freeze and thaw cycles. Experimental studies that report on histological changes after cryosurgery of bone were reviewed.

Chapter 3 presents an extended review of complications related to cryosurgical treatment of bone tumors, and **chapter 4** reports on complications in a retrospective study of 120 patients with bone tumors, treated cryosurgically at the University Medical Center (UMC) Nijmegen. Relevant series are exclusively published by experienced surgeons in the field of cryosurgery. Reported complications related to cryosurgery are deep wound infections, postoperative pathological fractures, nerve palsies, venous gas embolisms, and irreversible damage to the growth plate and the articular cartilage. The incidence of deep wound infections is approximately 4%, and sacral lesions are prone for developing an infection. Some technical items to avoid wound infections are the use of antibiotics peri-operatively, the use of suction drains to minimize wound haematoma, the prevention of accidental freezing of the skin, and the wound closure with adequate soft tissue coverage. Postoperative pathological fractures are of concern because of their frequency (overall incidence 11%). In addition to the bony destruction caused by the tumor, the revitalization process of the necrotic bone is held responsible for these

pathological fractures. Freezing of the epiphysis will result in irreversible damage, so close monitoring of the local temperature is recommended. However, it should be kept in mind that in clinical situations it will often not be clear whether the tumor itself, the cryosurgical procedure or both created a growth arrest. It seems that articular cartilage can resist low temperatures to some extent. Priority should be given to local tumor control; symptomatic osteoarthitis can be dealt with later on. Freeze-temperatures can result in nerve palsies that in general will resolve within 6 months time, provided that the nerve is anatomically intact.
In the year 1991, cryosurgery was introduced at the UMC Nijmegen for the treatment of active and aggressive benign, and low-grade malignant bone tumors. During surgery, local temperature was registered continuously to monitor the extent of the freeze. Except for the frequently (14%) encountered postoperative pathological fractures, the complication rate was comparable to other series reported in the literature. Implementation of titanium plate fixation, in lesions at risk for pathological fractures reduced this complication rate to approximately 4%. In general, complications will diminish not only along the learning curve of the physicians starting the new treatment, but also due to the improvement of the technique itself. This statement is confirmed by the decreasing incidence of prospectively registered complications of cryosurgically treated bone tumors at the UMC Nijmegen, since its introduction (Figure 10-1).

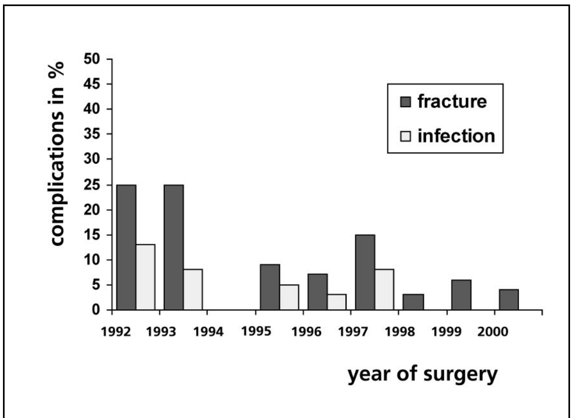

Figure 10-1. Prospectively registered percentage of pathological postoperative fractures and deep wound infections after cryosurgical treatment of 220 bone tumors at the University Medical Centre Nijmegen (UMCN), in the period 1992-2000. Notice the decreasing incidence of deep wound infections since cryosurgery was introduced at the UMCN in 1992, illustrating the effect of the learning curve of a physician starting a new treatment. Because of frequently encountered postoperative pathological fractures, preventive titanium plate fixation was gradually introduced for diaphyseal lesions. The number of pathological fractures observed declined.

2. *To study the local temperature field and thermodynamics in bone tissue during cryosurgery, and to relate the temperature field to the extent of necrosis.*

The results of a cryosurgical animal experiment, performed on rabbit femora were described in **chapter 5**. The temperature field in the cortical bone was recorded and related to the extent of osteonecrosis. Cooling rates close to the probe are high (>100°C/min), and there is an exponential drop in temperature with decreasing distance to the edge of the probe. At 60 sec freezing time, the "ice ball" will reach a margin of approximately 8 mm from the edge of the cryoprobe. Application of a tourniquet does not significantly alter the thermodynamics of the freeze/thaw cycles in the bone, if adequate surgical haemostasis of the operation field is obtained. It is concluded that three consecutive freeze-thaw cycles with a closed liquid nitrogen cryoprobe will result in an osteonecrotic margin extending up to the –10°C isotherm. Endosteum and periosteum, covering the cryosurgical lesion, are viable since they react with a overwhelming formation of immature bone at 1 week postoperatively. This resulted in a sleeve of bone around the diaphysis, three times the thickness of the cortex in width.

3. ***To examine the reduction of bone strength after cryosurgical treatment of long bones in time. To study the correlation between the mechanical characteristics of cryosurgically treated bone and its remodeling process.***

As stated in chapter 3 and 4, the frequent postoperative fractures after cryosurgical treatment of bone tumors are a point of interest. Literature reports on histological changes after cryosurgery of bone are numerous; but what's lacking are reports on bone strength. For this reason, an in vivo experiment on goat femora was conducted, of which the results were presented in **chapter 6**. Effects of cryosurgical treatment on bone strength were studied with time (0 to 26 weeks), and related to the remodeling process. It is concluded that torsional bone strength after cryosurgery is significantly ($p<0.001$) lower at 4 weeks (83% of controls), 7 weeks (77% of controls), and 10 weeks (82% of controls) postoperatively in this goat model compared with controls. This mechanical weakening can be explained by the remodeling process of the necrotic cortex, that leads to a longstanding increase in porosity. Another explanation for the reduced bone strength is given by the fact that cryosurgery causes a delay of local bone apposition; at 4 to 10 weeks the amount of bone apposition was significantly ($p<0.002$) lower compared with controls. Bone formation, most of all at the periosteal site, counteracts the weakening by the increased porosity by means of the formation of a sleeve of compact bone around the lesion. Prophylactic osteosynthesis of cryosurgically treated bone tumors is advised, especially for those tumors located in the diaphysis.

4. ***To study the influence of bone grafting on the healing of cryosurgically treated gap defects in long bones.***

After intralesional excision of a bone tumor with subsequent cryosurgery of the margin of the lesion, the defect is routinely reconstructed with cancellous bone grafts, especially in young patients where a biologic treatment is preferred. The intention of bone grafting is to accelerate the healing of the bone defect, which may shorten the rehabilitation period and reduce the risk for spontaneous fractures. Since cryosurgery induces necrosis and intra-vascular stasis, revascularization with subsequent incorporation of a bone graft may be prohibited. To define the role of bone grafting in the healing of cryosurgically treated gap defects of long bones, an in-vivo animal experiment was performed, as outlined in **chapter 7**. This study showed revascularization of an autologous morsellized bone graft despite the cryosurgical treatment; but this was followed by resorption and failed incorporation. Bone grafting did not contribute to a quicker recovery of torsional strength of the femoral diaphysis. It was assumed that the graft was stress shielded because of the rigidity of the gap defect in the femur, with resorption during the incorporation process as a result. Given the results of this study, the usefulness of bone grafting in intramedullary located bone tumors with minimal involvement of the endosteal lining of the cortex can be questioned. To arrive at a more rational application of bone grafting, further animal experiments should be conducted, focused on different type of lesions in relation to the bone graft incorporation.

5. *To report on further results of cryosurgically treated patients with fibrous dysplasia and giant cell tumor of bone.*

The application of cryosurgery in the management of fibrous dysplasia of bone (FD) and giant cell tumor of bone (GCT) was outlined in **chapters 8** and **9** respectively. Management and outcome in a diverse group of 20 patients with FD were described. The use of cryosurgery was not reported before in a comparable series of FD. Lesions were operated upon with the intention to resolve complaints, or to correct or prevent bony deformities. Intralesional excision of FD was nearly always combined with adjuvant cryosurgery, and reconstruction as necessary. Expected outcomes for circumscribed lesions were uniformly good. Extended lesions, though sometimes needing multiple operative procedures throughout the follow-up period showed satisfactory results. Extended lesions in McCune-Albright syndrome were associated with poor clinical outcomes. A favorable role of cryosurgery in the management of FD can not be concluded on the basis of this study.
In a retrospective study of 36 patient with GCT, treated by various techniques, the oncologic and functional outcome were determined. Intralesional excision with adjuvant cryosurgery resulted in satisfactory functional results with acceptable local tumor control. Extralesional excision guaranteed local tumor control, but at the cost of poor functional outcome in those cases with a wide excision. It is concluded that intralesional excision with local adjuvant therapy is the first chose of treatment for giant cell tumors of bone.

CLOSING REMARKS ON PROSPECTS FOR THE FUTURE

At this moment, cryosurgery has managed to secure a good position in the intralesional treatment of active and aggressive benign, and low-grade malignant bone tumors. A *state of the art* cryosurgical treatment results in good local tumor control with an acceptable complication rate, justifying a more widespread implementation in referral centers.

Cryosurgical technique

Additional studies are indicated to improve local tumor control by optimizing the cryosurgical technique. The current authors utilize a liquid nitrogen spray, an *open cryosurgical system*, to bring about the thermal damage. Advantage of this technique is the high cooling power, because the margin of the lesion is directly exposed to liquid nitrogen that vaporizes and extracts heat from the bone. Other benefits of a liquid nitrogen spray are the capability of freezing lesions with irregular surfaces, and the possibility to adjust the extent of the freeze relative to specific areas of the lesion. Draw-backs of this open technique are the accidental freezing of the skin and soft tissues by spill of liquid nitrogen, and the risk for venous gas embolisms. These adverse effects are promoted by the blocking of the extremities circulation during cryosurgery with a tourniquet. The use of a tourniquet, although ill advised, has the desirable effect of avoiding bloodshed in the operating field; free flow of blood within the lesion will have a negative effect on cryosurgical thermodynamics and cytotoxic capacity.

As an alternative, a *closed liquid nitrogen system* can be used to bring about the cold injury. In a closed system, one or more hollow probes through which liquid nitrogen circulates are used, so there is no risk for liquid nitrogen spill or venous gas embolisms. Recently, new cryosurgical probes are developed that produce lesions up to three times larger than similar sized probes previously available. A cryosurgical procedure of a bone tumor with the use of multiple cryoprobes, embedded in a saline gel to transmit the heat from the margin of the bony lesion to the probes, may probably be suitable to generate sufficient cooling power for an adequate cryosurgical margin, even in large and irregular lesions. If combined with the use of a tourniquet, there is no chance of a bloodshed with adverse effects on ice-ball formation. Compared with an open cryosurgical system, surgery with a closed system has a slow progress of the freeze events. This makes monitoring and control of the procedure easier. A comparative animal study should be conducted to further elucidate the efficiency of different cryosurgical techniques with respect to local tumor control, and then apply these methods in clinical areas. For this purpose, a tumor model has to be developed.

Magnetic Resonance guided cryosurgery

A significant limitation of thermocouple temperature monitoring is that the temperature can be monitored at only a few spatial locations. Ultrasound is an alternative method to image and monitor the ice-ball formation in soft tissues. But recently, Magnetic Resonance (MR) imaging techniques demonstrated superior ice/tissue contrast in monitoring slow elapsing cryosurgical procedures of soft tissue tumors with a closed system. MR imaging techniques can delineate the size and shape of the ice-ball in soft tissues. Furthermore, a MR imaging assisted numerical technique is available that can calculate and display the two dimensional temperature distribution in the frozen soft tissue region on a standard MR image. The use of multiple probes in clinical cryosurgery will substantially limit these numerical techniques. Preliminary data were published, indicating the dependence of the MR signal on temperature in frozen soft tissues, provided that sufficiently short echo times are used. Efforts should focus on this opportunity. This MR guided technique has the potential for clinical introduction in the near future, but efforts should also focus on the development of safe, MR compatible probes with an increased cooling power.

Computed tomography

Computed tomography (CT) may give new opportunities to the orthopaedic surgeon involved in cryosurgery of bone tumors.

First of all, CT is a tool to evaluate the cryosurgical margin of bone in retrospect. By quantitative assessment of tomograms, made a few weeks after surgery, the cryosurgical margin of the bone can be deduced from the locally increased porosity of the necrotic cortex. This gives the surgeon feedback information about his cryosurgical procedure.

Secondly, repeated CT measurements several months after cryosurgery will enable the physician to quantify the apposition of new bone at the remaining cortex of the lesion. The availability of this information may extent our knowledge of the healing response of the bone and the possible related co-factors, and may form the reason for new innovative research to improve the cryosurgical technique. A better understanding of the process of bone apposition is essential, since this biological response is of utmost importance for the recovery of the mechanical integrity of the bony lesion after cryosurgical treatment.

In the third place, computed tomography of bone tumors supplies the physician with data suitable for computerized modeling, aimed at quantification of the mechanical integrity of the affected bone. This presents a rational basis for decision making on operative and postoperative

management, such as the issue whether or not preventive osteosynthesis is indicated. At the moment, computer simulation is a time consuming work. Efforts should focus on the development of automated and fast model generation from patient specific data.
This is an argument for physicians to work in close association with radiologists, biomechanical engineers, and information technologists.

Healing process
Following intralesional excision of a bone tumor, cryosurgery of the margin will further weaken the remaining bone stock, because of increased porosity during the long-lasting remodeling process of the osteonecrotic lesion. On the short term, this mechanical weakening of the affected bone is counteracted by the apposition of new bone, predominantly at the periosteal site. In clinical practice, the weakening of the bone stock reveals itself in the occurrence of postoperative pathological fractures. A solution to this clinical problem is preventive osteosynthesis.
On the other hand, one could wonder whether the local bone apposition could be promoted somehow or other, to make osteosynthesis redundant. Innovative animal experiments have to be conducted for this purpose, to look for stimuli that will trigger the formation of subperiosteal bone. Further clarification of the efficacy of bone grafts in cryosurgical lesions follows naturally from this line of investigation. Future experimental studies on incorporation of bone grafts should focus on the role of the mechanical properties of the lesion.

Cryoablation of inoperable tumors
Cryoablation, in situ freezing of a tumor through insertion of cryoprobes to achieve devitalization and tumor control, is a valid approach to the treatment of liver metastases and prostate neoplasm's. Because of good experience with cryoablation of these tumors, one could wonder if the indication for cryoablation can be expanded to the treatment of inoperable soft tissue sarcomas. Preliminary data were published in this field, reporting on feasibility and safety of cryosurgical ablation. One or more closed cryoprobes are inserted into the tumor that is minimally exposed. So far, cryoablation was successful, and well tolerated by patients. The role of cryoablation, in conjunction with other modalities in the treatment of soft tissue sarcomas, needs to be elucidated.
Cryosurgery has a special place in the treatment of bone tumors of the spine. Spinal bone tumors are located close to the spinal cord or nerve roots, and marginal excision will often not be feasible without the generation of invalidating morbidity. There are prospects for intralesional excision and adjuvant cryosurgery of these inoperable tumors, on the condition that the neural structures can be protected from the cold injury. For this purpose, specific cryosurgical techniques to secure safety and effectiveness must be developed. One can conceive the evolution of a continuous warmth irrigation system to protect the spinal cord.

SAMENVATTING

BESCHOUWING VAN DE DOELSTELLINGEN

EN AFSLUITENDE OPMERKINGEN

GERICHT OP DE TOEKOMST

SAMENVATTING

Cryochirurgie kan als een locale aanvullende behandeling toegepast worden bij intralesionale excisie van actieve en agressieve goedaardige en laaggradig kwaadaardige bottumoren. Het doel van deze aanvullende (adjuvante) behandeling is het verkleinen van de kans op een locaal tumorrecidief, door de celdodende werking van zeer lage temperaturen op de achtergebleven tumorcellen ter plaatse van de chirurgische marge. Eind jaren zestig zijn door enkele auteurs veelbelovende resultaten beschreven van adjuvante cryochirurgische behandeling van bottumoren. Desondanks is cryochirurgie niet algemeen toegepast, waarschijnlijk vanwege berichten over veelvuldige complicaties.
Dit proefschrift handelt over complicaties bij cryochirurgische behandeling van bottumoren, over dierexperimenten gericht op het gedrag van cryochirurgisch behandeld bot en over klinische resultaten van cryochirurgische behandeling van fibreuze dysplasie en reusceltumoren van bot.
Aansluitend op de inleiding, worden in **hoofdstuk 1** de doelstellingen van het proefschrift geformuleerd. Het volgende is een samenvatting van de resterende hoofdstukken, toegespitst op de doelstellingen.

DOELSTELLINGEN

1. Het beschrijven en bediscussiëren van de complicaties die gerelateerd zijn aan de aanvullende cryochirurgische behandeling van bottumoren.

Hoofdstuk 2 handelt over cryobiologie, de studie van fysieke effecten van lage temperaturen op levend weefsel. Basale principes die bij een cryochirurgische behandeling de celdood bevorderen zijn (1) krimpen van de cel met verhoging van de zout concentraties, (2) intracellulaire ijsvorming met mechanische beschadiging van celorganellen en celmembraan, (3) mechanische cel beschadiging door voortgaande ijs vorming, (4) re-kristallisatie met de vorming van grote ijskristallen tijdens de dooi fase en (5) ischaemie van de weefsels door obstructie van de microcirculatie. Om in de praktijk een effectieve cryochirurgische behandeling van bottumoren uit te voeren dient rekening gehouden te worden met de volgende technische aspecten: (1) een snelle bevriezing van tenminste 100°C/min, (2) een minimale vriestemperatuur van –50°C bij de periferie van de cryochirurgische marge, (3) het aanhouden van de vriestemperatuur gedurende een periode, (4) een spontane, geleidelijke en complete opwarming en (5) het herhalen van vries/dooi cyclus. Er volgt een uiteenzetting van experimentele studies die de histologische veranderingen van bot in reactie op cryochirurgie beschrijven.
De aan cryochirurgie gerelateerde complicaties worden in **hoofdstuk 3** uiteengezet. In **hoofdstuk 4** wordt een retrospectieve patiëntenstudie beschreven naar de complicaties bij 120 cryochirurgisch behandelde bottumoren in het Universitair Medisch Centrum (UMC) St. Radboud.
Relevante klinische studies zijn uitsluitend gepubliceerd door orthopaedisch chirurgen met ruime ervaring op het gebied van cryochirurgie. De aan cryochirurgie gerelateerde complicaties zijn, diepe wondinfecties, postoperatieve spontane fracturen, zenuwuitval, veneuze stikstofgas embolieën en irreversibele schade van de groeischijf of het gewrichtskraakbeen. Diepe wondinfecties hebben een incidentie van ongeveer 4% en worden met name waargenomen bij

afwijkingen gelokaliseerd in het sacrum. Enkele aspecten die mogelijk bijdragen aan het verminderen van de kans op een diepe wondinfectie zijn: het gebruik van peri-operatieve antibiotica profylaxe, het plaatsen van wonddrains, het voorkomen van iatrogeen vriesletsel van de huid en weke delen en het zorgvuldig sluiten van de wond met adequate weke delen bedekking. Een punt van zorg zijn de postoperatieve pathologische fracturen die frequent optreden (incidentie 11%). Het ontstaan van deze pathologische fracturen wordt niet alleen geweten aan de aantasting van het bot door de tumor en operatie, maar ook aan het revitalisatieproces van het door cryochirurgie ontstane dode (necrotische) bot. Bij cryochirurgie van een in de nabijheid van een groeischijf gelokaliseerde bottumor is peroperatieve monitoring van de locale temperatuur van wezenlijk belang, aangezien bevriezing van de groeischijf irreversibele schade veroorzaakt. In de praktijk is het vaak niet duidelijk of een groeistoornis het gevolg is van een iatrogeen vriesletsel of van aantasting door de expansief groeiende tumor op zich. De indruk bestaat, dat gewrichtskraakbeen in enige mate bestand is tegen vrieskoude. Bij de behandeling van bottumoren die aan een gewricht grenzen dient prioriteit gesteld te worden aan het verkrijgen van locale tumorcontrole; een eventuele resulterende arthrose op termijn is van secundair belang. Bevriezing van zenuwen leidt tot zenuwuitval, waarbij er veelal binnen 6 maanden een spontaan herstel optreedt, vooropgesteld dat de zenuw anatomisch intact is.
In 1991 werd cryochirurgie in het UMC St Radboud geïntroduceerd als locale aanvullende behandeling bij intralesionale excisie van actieve en agressieve goedaardige en laaggradig kwaadaardige bottumoren. Peroperatieve registratie van de locale temperatuur werd als hulpmiddel gehanteerd om het vriesletsel te doseren. Met uitzondering van de frequent optredende postoperatieve pathologische fracturen (14%), was het complicatie percentage in overeenstemming met vergelijkbare klinische studies in de literatuur. Modificatie van de operatietechniek, door de invoering van preventieve plaatosteosynthese bij risicopatiënten, heeft het optreden van postoperatieve pathologische fracturen gereduceerd tot ongeveer 4%. Prospectieve registratie van de cryochirurgisch behandelde patienten in het UMC St Radboud toont aan dat de incidentie van complicaties met de jaren afneemt. De leercurve, die vanaf de introductie van een nieuwe techniek door de chirurg wordt doorlopen, alsmede de aanpassingen van de chirurgische techniek spelen hierbij een rol.

2. Het bestuderen van de locale temperatuursveranderingen in het botweefsel tijdens cryochirurgie en het relateren van de uitbreiding van de botnecrose aan de locale temperatuur.

De resultaten van in-vivo dierexperimenten bij konijnen worden beschreven in **hoofdstuk 5**. Bij een cryochirurgisch model van het femur wordt de locale temperatuur in het botweefsel gemeten en gerelateerd aan de uitbreiding van botnecrose. Op korte afstand van de cryoprobe daalt de temperatuur van het botweefsel snel (> 100°C/min). De temperatuur van het bot daalt exponentieel naarmate de afstand tot de cryoprobe afneemt. Een vriesduur van 60 seconden resulteert in een "ijsbal" met een marge van ongeveer 8 mm rondom de cryoprobe. Het gebruik van een tourniquet heeft geen significant effect op de thermodynamica tijdens cryochirurgie, vooropgesteld dat adequate haemostase in het wondgebied is verkregen. Geconcludeerd wordt dat drie opeenvolgende cryochirurgische cycli van botweefsel met een gesloten cryoprobe aanleiding geven tot botnecrose in een gebied waarvan de marge zich uitstrekt tot de -10°C isotherm. Het periosteum en endosteum, die de necrotische cortex bedekken reageren met een overmatige vorming van jong botweefsel in één week tijd. Hierdoor ontstaat er ter plaatse van de cryochirurgische laesie een mantel van botweefsel rondom de schacht van het femur, met een dikte van drie maal de oorspronkelijke dikte van de cortex.

3. Het bestuderen van de afname van botsterkte, in verloop van tijd, na cryochirurgische behandeling van lange pijpbeenderen. Het relateren van de botsterkte aan het proces van remodellering van de botnecrose.

Zoals aangegeven in hoofdstuk 4 en hoofdstuk 5, zijn de frequent optredende pathologische fracturen na cryochirurgische behandeling van bottumoren een punt van zorg. Meerdere studies zijn gepubliceerd over de histologische veranderingen die optreden na cryochirurgie van bot, maar gaan voorbij aan de botsterkte. Het dode bot wordt gerevasculariseerd en ondergaat vervolgens een remodelleringsproces, waarbij geleidelijk aan de necrotische botmatrix wordt vervangen door nieuw vitaal botweefsel. **Hoofdstuk 6** beschrijft de resultaten van een in-vivo onderzoek bij geiten femora naar de mechanische eigenschappen van cryochirurgisch behandeld bot. Op verschillende tijdstippen (0 tot 26 weken) na cryochirurgische behandeling van een circulair defect van de femurschacht, werd de botsterkte bepaald en gerelateerd aan het remodelleringsproces. Vergeleken met de controledieren was de botsterkte significant verminderd bij 4 weken (83% t.o.v. de controlegroep), 7 weken (77% t.o.v. de controlegroep) en 10 weken (82% t.o.v. de controlegroep) na operatie. De verzwakking van het bot kan verklaard worden met het remodelleringsproces van de door cryochirurgie geïnduceerde botnecrose, hetgeen gepaard gaat met een toename van de porositeit van de botmatrix. De vertraagde afzetting van nieuw botweefsel ter plaatse van het cryochirurgisch behandelde defect is een aanvullende verklaring; bij 4, 7 en 10 weken was de hoeveelheid botafzetting significant minder in vergelijking met de controlegroep. De afzetting van nieuw botweefsel vindt voornamelijk plaats aan de periostale zijde van de cortex en geeft aanleiding tot de vorming van een mantel van botweefsel rondom de schacht. Dit compenseert de mechanische verzwakking van de necrotische cortex, die optreedt tijdens remodellering. Bij aanvullende cryochirurgische behandeling van bottumoren, met name van tumoren gelokaliseerd in gewichtsdragende pijpbeenderen, dient preventieve osteosynthese overwogen te worden.

4. Het bestuderen van het stimulerende effect van bottransplantatie op de genezing van cryochirurgisch behandelende defecten in pijpbeenderen.

Bij intralesionale excisie van bottumoren met aanvullende cryochirurgie van de marge wordt het defect routinematig opgevuld met een spongieus bottransplantaat. Vooral bij jonge patiënten geniet een biologische reconstructie van het defect de voorkeur. Het doel van een bottransplantaat is het bespoedigen van het herstel van het botdefect, waardoor de revalidatieperiode verkort kan worden en de kans op pathologische fracturen eventueel vermindert. Omdat cryochirurgie aanleiding geeft tot weefselnecrose en obstructie van de locale bloedvaten, kan verondersteld worden dat een bottransplantaat in een dergelijk wondbed niet goed revasculariseert en incorporeert. Om het effect van een bottransplantaat op de genezing van cryochirurgisch behandelde botdefecten te bestuderen, is een in-vivo experiment uitgevoerd bij femora van geiten. Deze studie, waarvan de resultaten in **hoofdstuk 7** zijn weergegeven, toonde aan dat een autoloog bottransplantaat, als spongieuze botsnippers geïmpacteerd in een cryochirurgisch behandeld botdefect, mogelijk wel revasculariseert maar vervolgens niet verder incorporeert. Bottransplantatie resulteerde niet in een sneller herstel van de botsterkte van de femurschacht. Verondersteld werd dat de stijfheid van het botdefect aanleiding gaf tot stress-shielding van het transplantaat en hiermee de grondslag vormde voor het resorberen van het bottransplantaat. Gezien de resultaten van deze studie kan getwijfeld worden aan het nut van routinematige bottransplantaties bij cryochirurgisch behandelde bottumoren. Verder dierexperimenteel onderzoek met andere modellen zal nodig zijn om inzicht te verkrijgen in welke situaties incorporatie van het bottransplantaat te verwachten is.

5. Het beschrijven van de klinische resultaten van aanvullende cryochirurgische behandeling aan de hand van een groep patiënten met fibreuze dysplasie en een groep patiënten met reusceltumoren van het bot.

In **hoofdstuk 8** worden de behandeling en resultaten besproken van fibreuze dysplasie van het bot, aan de hand van een inhomogene groep van 20 patiënten met 32 klinisch significante localisaties van fibreuze dysplasie. Doel van operatieve behandeling bij deze patiënten was het behandelen van pijnklachten, het corrigeren en/of voorkomen van deformiteiten van de pijpbeenderen. Intralesionale excisie van de fibreuze dysplasie werd bijna altijd gevolgd door een aanvullende cryochirurgische behandeling en indien nodig een reconstructie van de laesie. De resultaten waren uniform goed bij circumstripte laesies van fibreuze dysplasie. Uitgebreide laesies gaven eveneens een goed resultaat, alhoewel enkele patiënten meerdere operaties ondergingen gedurende de follow-up periode. Uitgebreide laesies van fibreuze dysplasie die geassocieerd waren met het McCune-Albright syndroom hadden een slecht resultaat. Op basis van deze studie kan niet geoordeeld worden over het effect van adjuvante cryochirurgie bij de behandeling van fibreuze dysplasie van het bot.
In **hoofdstuk 9** wordt een retrospectieve studie beschreven van 36 patiënten die op diverse wijzen zijn behandeld voor een reusceltumor van het bot. Intralesionale excisie met aanvullende cryochirurgie van de reusceltumor gaf een goed functioneel resultaat met een acceptabele locale tumorcontrole. Extralesionale excisie van de reusceltumoren was een garantie voor locale tumorcontrole, maar ging gepaard met een slecht functioneel resultaat in het geval van een ruime chirurgische marge. Gesteld werd dat intralesionale excisie van reusceltumoren van het bot te prefereren is boven extralesionale excisie. De auteurs geven de voorkeur aan cryochirurgie als vorm van locale aanvullende behandeling.

AFSLUITENDE OPMERKINGEN GERICHT OP DE TOEKOMST

Cryochirurgie is een erkende vorm van locale aanvullende behandeling bij actieve en agressieve goedaardige en laaggradig kwaadaardige bottumoren. Met een aanvullende cryochirurgische behandeling wordt een goede locale tumorcontrole verkregen met acceptabele complicaties, zodat toepassing in meerdere centra gerechtvaardigd is.

Cryochirurgische techniek

De aandacht dient in de toekomst gericht te blijven op het verbeteren van de cryochirurgische techniek teneinde de kans op een locaal tumorrecidief te verminderen. Cryochirurgie bij de patiënten, beschreven in dit proefschrift, vond plaats met een vloeibare stikstofspray, een *open systeem*. Een voordeel van een open systeem is het grote koelend vermogen; de vloeibare stikstof komt in direct contact met de marge van de laesie en onttrekt daardoor veel warmte aan het bot tijdens de verdamping. Andere voordelen van een open systeem zijn, de mogelijkheid om onregelmatige oppervlakten te vriezen en de mogelijkheid om selectief de dosering van het vriesletsel in bepaalde gebieden van de laesie aan te passen. Bij vriezen met een open systeem bestaat er gevaar voor veneuze stikstofgas embolieën en kan er een ongewenst vriesletsel optreden van de huid of andere weke delen door het morsen van vloeibare stikstof. Bij gebruik van een tourniquet om de extremiteit zullen deze nadelige effecten in versterkte mate optreden. Een tourniquet, alhoewel afgeraden in combinatie met een open cryochirurgisch systeem, blokkeert de circulatie en voorkomt hiermee het diffuse bloeden in het operatiegebied. Het vrij stromen van bloed in de laesie beïnvloedt de thermodynamica tijdens de vriesprocedure in negatieve zin en leidt tot een afname van het celdodend vermogen.
Het alternatief voor een vloeibare stikstofspray is een gesloten cryoprobe, een *gesloten systeem*. Bij een gesloten systeem worden één of meerdere holle probes, waar doorheen vloeibare stikstof stroomt, gebruikt om de tumor te bevriezen zodat er geen kans bestaat op het accidenteel vriezen van de weke delen of het optreden van gasembolieën. Recent ontwikkelde gesloten cryoprobes geven een cryochirurgische marge die drie maal zo groot is als bij de voormalige cryoprobes. Met meerdere gesloten cryoprobes, eventueel ingebed in een zouthoudende gel om de warmte van de marge van de tumor naar de cryoprobe te geleiden, kan waarschijnlijk voldoende vriescapaciteit gegenereerd worden om bij grote en onregelmatig begrensde bottumoren een adequate cryochirurgische marge te verkrijgen. Tevens kan met gelijktijdig gebruik van een tourniquet het negatieve effect van bloedingen in het operatieterrein op de vorming van een ijsbal vermeden worden. In vergelijking met een open systeem verloopt de vriesprocedure met een gesloten cryoprobe geleidelijker. Vervolgen en controleren van de cryochirurgie is hiermee gemakkelijker. Vergelijkende dierstudies zijn gewenst om meer inzicht te verkrijgen in de effectiviteit van de verschillende cryochirurgische technieken voor wat betreft locale tumorcontrole.

Magnetic Resonance gecontroleerde cryochirurgie

Controle van de cryochirurgische procedure van bottumoren met thermocouples heeft zijn beperkingen vanwege de plaatselijke metingen. Echografie, waarmee de vorming van een ijsbal in de weke delen adequaat vervolgd kan worden, is van geen waarde voor het controleren van de cryochirurgische procedure in botweefsel. Recente ontwikkelingen op het gebied van Magnetic Resonance Imaging (MRI) maken een uitstekend contrast haalbaar bij de beeldvorming van een ijsbal tijdens een geleidelijke vriesprocedure van weke delen met een gesloten cryoprobe. Bovendien is een numerieke techniek voorhanden waarmee een twee-dimensionaal temperatuurspatroon berekend en weergegeven kan worden op een routine MRI afbeelding. Deze numerieke techniek is niet toepasbaar bij gebruik van meerdere cryoprobes tegelijk. Voorlopige resultaten zijn gepubliceerd over een relatie tussen het Magnetic Resonance signaal en de temperatuur van bevroren weke delen, vooropgesteld dat voldoende korte echotijden worden gebruikt. De aandacht dient op deze mogelijkheden gevestigd te worden. Magnetic Resonance gecontroleerde cryochirurgie heeft het potentieel voor toekomstige klinische toepassing, maar niet voordat MRI compatibele cryoprobes met voldoende capaciteit zijn ontwikkeld.

Computer tomografie

Computer tomografie (CT) kan van waarde zijn voor de orthopaedisch chirurg die betrokken is bij de cryochirurgische behandeling van bottumoren.

Ten eerste, kan CT een hulpmiddel zijn om retrospectief de cryochirurgische marge in het botweefsel te bepalen. Met kwantitatieve analyse van een CT scan, gemaakt enkele weken na de operatie, is de cryochirurgische marge te beoordelen aan de hand van de toegenomen locale porositeit van de necrotische cortex. Hiermee krijgt de chirurg directe terugkoppeling over de kwaliteit van de behandeling.

Ten tweede, kan gedurende de follow-up periode met CT onderzoek de afzetting van nieuw bot tegen de cryochirurgisch behandelde ossale laesie worden gekwantificeerd. Met dergelijke informatie kan meer kennis vergaard worden over de genezingscapaciteit van bot en de daaraan gerelateerde co-factoren. Dit vormt een grondslag voor verder onderzoek gericht op het stimuleren van locale botafzetting en optimalisatie van de chirurgische behandeling. De locale botafzetting tegen het cryochirurgisch behandelde bot is van essentieel belang voor het herstel van de mechanische integriteit van het aangedane bot.

Ten derde, levert CT onderzoek van een bepaalde bottumor data op die gebruikt kunnen worden voor computer simulaties gericht op de mechanische eigenschappen van het aangedane bot. Operatiestrategieën alsmede het postoperatief beleid kunnen hierop afgestemd worden, zoals bijvoorbeeld de noodzaak van preventieve osteosynthese. Tot op heden is computer simulatie een tijdrovende bezigheid. In de nabije toekomst is behoefte aan geautomatiseerde en snelle modelvorming van patiënt specifieke data.

Hiermee wordt een pleidooi gevoerd voor een nauwe samenwerking tussen de chirurg, de radiodiagnost, de biomechanicus en de informaticus.

Genezingsproces

Aanvullende cryochirurgie bij intralesionale excisie van bottumoren zal aanleiding geven tot verdere verzwakking van het bot ten gevolge van een toename van de porositeit in de cryochirurgische marge. Afzetting van nieuw botweefsel ter plaatse van de cryochirurgische laesie compenseert ten dele voor de verzwakking van het revitaliserende dode bot. Dat er sprake is van een relevante verzwakking van het cryochirurgisch behandelde bot wordt onderstreept door het frequent optreden van postoperatieve pathologische fracturen in de kliniek en de resultaten van dierexperimenten beschreven in dit proefschrift. Een oplossing voor dit probleem is het uitvoeren van een preventieve osteosynthese tijdens de operatie. Aan de andere kant kan men zich afvragen of er mogelijkheden bestaan om de locale botafzetting te stimuleren, zodat preventieve osteosynthese overbodig wordt. Wellicht dat met behulp van dierexperimenten technieken ontwikkeld kunnen worden die de vorming van botafzetting bevorderen. In dezelfde onderzoekslijn kan het effect van bottransplantatie op het herstel van de mechanische integriteit van een cryochirurgisch behandelde laesie bestudeerd worden.

Cryoablatie van inoperabele tumoren

Cryoablatie, het vernietigen van tumoren door in situ bevriezing met cryoprobes, is een erkende behandelingmethode voor levermetastasen en prostaatcarcinomen. Vanwege de goede ervaringen reist de vraag of het indicatiegebied voor cryoablatie uitgebreid kan worden met inoperabele weke delen sarcomen, omdat deze in het algemeen niet gevoelig zijn voor chemotherapie of radiotherapie. Eerste ervaringen omtrent de haalbaarheid en veiligheid van cryoablatie van weke delen sarcomen zijn onlangs gepubliceerd. Via een minimale exposure

werden één tot meerdere cryoprobes in de tumor gepositioneerd. De procedure werd door de patiënten goed doorstaan en leidde tot locale tumorcontrole. De mogelijkheden van cryochirurgie op dit terrein dienen verder ontwikkeld te worden.
Voor de behandeling van bottumoren van de wervelkolom is cryochirurgie van bijzondere waarde, omdat marginale excisie van tumoren veelal niet mogelijk is zonder compromitatie van het nabijgelegen ruggenmerg of zenuwwortels, met gevaar voor een invaliderende morbiditeit. Intralesionale excisie met adjuvante cryochirurgie is dan een optie voor deze inoperabele tumoren, vooropgesteld dat de neurale structuren adequaat tegen het koudeletsel beschermd kunnen worden. Voor effectieve en veilige cryochirurgie dient een specifieke operatietechniek ontwikkeld te worden. Hierbij kan gedacht worden aan een irrigatiesysteem dat het ruggenmerg en de zenuwwortels beschermt.

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CURRICULUM VITAE

Lucien Keijser was born on April 8, 1964, in Mook en Middelaar, The Netherlands. After graduating from high school (Bernardinuscollege, Heerlen, The Netherlands) in 1982, he started his medical training at the University of Leiden. In 1992 he registered as Doctor of Medicine.

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