Cryosurgical Ablation of Bone Tumors

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BACKGROUND

Cryosurgical Ablation is the therapeutic application of cold in situ to induce tissue necrosis with curative intent. Cryosurgical ablation performed by direct pouring of liquid nitrogen is an effective adjuvant to ablation in the management of a large variety of bone tumors, including benign-aggressive, metastatic, and primary malignant lesions. It is an intraleisional procedure, which permits the avoidance of major resection and associated loss of function.

Cryosurgical ablation is a very powerful technique. It weakens the bone surrounding the tumor cavity and, when not used judiciously, may cause additional soft tissue injuries. Awareness of these potential complications has led to refinement of surgical practices to include soft tissue protection, stable reconstruction, the use of perioperative antibiotics, and enhancement of rehabilitation protocols for gradual weight bearing. These guidelines have resulted in a gratifyingly low rate of complications and rendered this treatment a safe and reliable modality.

It may be expected that cryosurgical ablation will no longer be the exclusive practice of a relatively small group of surgeons and that it will eventually enjoy greater popularity in the not too distant future.

Historical Aspects and Physiologic Background

Although cryosurgical ablation had been used in the 1850s for the management of locally advanced carcinoma of the cervix, its application to the management of bone tumors was not assessed until more than a century later, in the classic 1966 animal study by Gage et al., in which the femora of living mongrel dogs were frozen by perfusing liquid nitrogen through encircling latex coils. Liquid nitrogen, which has a boiling temperature of $-196^\circ$C, allowed rapid freezing of a 2-cm rim of bone around these coils. Using histopathologic studies and plain radiographs, the authors documented the occurrence of tissue necrosis and bone resorption that was associated with mechanical weakening and spontaneous fractures.

These changes, however, were followed by new bone formation that developed slowly, starting from the vital bone at the periphery; it was first observed at 2 months and reached its peak at 6 months after freezing.

Although only normal bone was investigated in their experiment, Gage et al speculated that cold allows for nonspecific cell destruction and may induce tumor kill as well. They further suggested the use of intraleisional cryosurgical ablation in lieu of tumor resection or amputation. The use of this technique in the management of human bone tumors was first reported in 1969.

Following curettage of a metastatic bone lesion, Marcove and Miller poured liquid nitrogen into the tumor cavity with the intent of inducing tumor necrosis and avoiding the need for extensive resection and reported having achieved both goals.

Further studies confirmed and refined the initial findings of Gage et al. and showed that temperatures between $-21^\circ$C and $-60^\circ$C are needed to obtain cell necrosis; temperatures below $-60^\circ$C exerted no further lethality.

A number of mechanisms have been found to be responsible for the tissue necrosis induced by cryosurgical ablation. These mechanisms can be grouped into two categories: immediate and delayed.

Four mechanisms are involved in the immediate cytotoxicity produced by cryosurgical ablation: (1) formation of ice crystals and membrane disruption; (2) thermal shock; (3) dehydration and toxic effects of electrolyte changes; and (4) denaturation of cellular proteins. The formation of intracellular ice crystals is considered as being the main mechanism of immediate cellular necrosis.

The two mechanisms most likely responsible for the delayed, progressive necrosis that is observed following cryosurgical ablation and for the problems associated with subsequent repair of frozen tissue are (1) the damage to the microvascular circulation and (2) vascular stasis.

During cryosurgical ablation, ice crystals first occur in the extracellular spaces. The withdrawal of water from the system into these crystals creates a hyperosmotic extracellular environment, which, in turn, draws water from the cells. As the process continues, these crystals grow, the cells shrink and dehydrate, electrolyte concentration is increased, and membranes and cell components are damaged. Because rapid freezing, such as that achieved by direct pour of liquid nitrogen, does not allow sufficient time for the withdrawal of water from the cells, intracellular ice crystals are formed simultaneously.

Conversely, a slow thaw will cause intracellular recrystallization of the already formed crystals and membrane disruption, whereas a rapid thaw will not.

Repeated freeze–thaw cycles also increase the extent of tissue necrosis because of the improved cold conductivity following the first cycle. Therefore, repeated cycles of rapid freezing and spontaneous thaw achieve the maximal effect of cell necrosis.

Histologically, the most dramatic effect of cryosurgical ablation is on the appearance of the bone marrow: a rim of 1 to 2 cm of extensive necrosis with minimal inflammatory response appears following direct pour of liquid nitrogen. This is followed by liquefaction and progressive fibrosis. Large, thickened, and thrombosed vessels occasionally are seen as well.

INDICATIONS

Histologic Diagnoses

Benign-aggressive bone tumors

- Giant cell tumor
- Aneurysmal bone cyst
- Simple bone cyst
- Fibrous dysplasia
- Enchondroma
- Chondroblastoma
- Eosinophilic granuloma
Part 4 ONCOLOGY • Section I  SURGICAL MANAGEMENT

- Osteoblastoma
- Chondromyxoid fibroma
- Low-grade sarcomas of bone
- Low-grade chondrosarcoma
- Metastatic tumors

Morphologic Criteria
- Cryoablation is appropriate for periarticular and sacral lesions in which the circumferential rim of the cortex that remains after tumor removal can hold liquid material and is adequate to ensure a mechanically stable reconstruction.

SURGICAL MANAGEMENT
- Cryosurgical ablation is carried out in five stages: (1) tumor exposure; (2) thorough curettage; (3) high-speed burr drilling of the tumor cavity; (4) cryoablation; and (5) mechanical reconstruction.

DIRECT POUR LIQUID NITROGEN
- When technically possible, a pneumatic tourniquet is used during the procedure to decrease local bleeding and prevent blood from acting as a heat sink and posing a thermal barrier to cryoablation.
- A large cortical window the size of the longest longitudinal dimension of the tumor is made after exposure of the involved bone. It must be elliptical, with its axis parallel to the long axis of bone, to reduce the stress rising effect (TECH FIG 1A–C).

- All gross tumor material is removed with hand curettes (TECH FIG 1D–E). This is followed by high-speed burr drilling of all remaining macroscopic disease and the walls of the tumor cavity (TECH FIG 1F).
- Bony perforations are identified and sealed with Gelfoam (Upjohn, Kalamazoo, MI) before introduction of the liquid nitrogen. The neurovascular bundle and fasciocutaneous flaps are protected by mobilization and by shielding (with surgical pads) from direct contact with the liquid nitrogen, after which cryoablation is performed.

TECH FIG 1 • A. Plain radiograph showing aneurysmal bone cyst of the proximal humerus. B. The tumor site is widely exposed by a deltopectoral incision, and fasciocutaneous flaps are mobilized to expose the entire extent of the tumor. C. A large cortical window the size of the longest longitudinal dimension of the tumor is made. D. Plain radiograph showing giant cell tumor of the distal femur. E. The tumor is first removed with hand curettes. This should be meticulously performed, leaving only residual microscopic disease in the tumor cavity. (continued)
Curettage is followed by high-speed burr drilling.

The traditional technique of cryoablation entails direct pour of liquid nitrogen through a stainless steel funnel into the tumor cavity, taking care to fill the entire cavity (TECH FIG 2). Thermocouples are used to monitor the freeze within the cavity, cavity wall, adjacent soft tissues, and an area 1 to 2 mm from the periphery of the cavity. The surrounding soft tissues are irrigated continuously with warm saline solution to decrease the possibility of thermal injury.

Freezing (boiling of liquid nitrogen) lasts 1 to 2 minutes and is proportional to the volume of poured liquid nitrogen. It is followed by spontaneous thaw, which occurs over 3 to 5 minutes. The cycle is considered complete once the temperature of the cavity rises above 0°C. The cavity is irrigated with saline after two freeze–thaw cycles have been carried out. At this point, the process of reconstructing the tumor cavity begins.

Reconstruction includes the use of internal fixation and the use of polymethylmethacrylate (PMMA; TECH FIG 3). Subchondral surfaces are reinforced with autologous bone graft before cementation.

CLOSED CRYOABLATION WITH ARGON GAS

Cryoablation using direct pour of liquid nitrogen has several technical drawbacks. First, after it has been poured, there is no control of the overall freezing time or of the temperature at different sites within the tumor cavity. Second, it is a gravity-dependent procedure, ie, the poured liquid cannot reach corners of the tumor cavity that are positioned above the fluid level.

In response to these problems, closed cryoablation using argon gas was developed and became available in the late 1990s. This approach entails filling the tumor cavity with a gel medium, inserting metal probes into the gel, and executing computer-controlled delivery of argon gas through the metal probes.

Argon gas serves as the freezing agent, and the surrounding gel acts as a conducting medium, which distributes the low temperature equally throughout the tumor cavity (TECH FIGS 4, 5, and 6).

Computer-controlled delivery of argon gas allows determination of both the desired temperature throughout the tumor cavity and the overall freezing time, and the use of a viscous gel enables filling of any shape of tumor cavity, regardless of gravity considerations (TECH FIG 7).
Reconstruction includes cemented hardware and reinforcement of subchondral surfaces with autologous bone graft. This principle of reconstruction is applied in all anatomic locations: proximal femur (A), distal femur (B), proximal tibia (C), distal tibia (D), distal radius (E), and proximal ulna (F).
Chapter 6  CRYOSURGICAL ABLATION OF BONE TUMORS

TECH FIG 4 • A. Different sizes of metal probes used for delivery of argon gas. B. The tumor cavity filled with gel medium and the metal probe within it. C. The gel freezes and creates an ice ball within a few seconds after perfusion of the argon gas through the probe.

TECH FIG 5 • A. Plain radiograph showing a giant cell tumor of the proximal tibia. B. Curved incision along the lateral tibial metaphysis. C. Curettage. D. High-speed burr drilling. E. An ice ball is formed around the tip of the probes on perfusion of argon gas.

TECH FIG 6 • A. Recurrent low-grade chondrosarcoma of the distal radius. B. Tumor curettage. C. High-speed burr drilling. (continued)
**TECH FIG 6 (continued)** D. The tumor cavity is filled with gel. E. Cryoablation.

**TECH FIG 7** Cryoablation of the proximal ulna (A) and the fourth toe (B) using the closed, argon-based system. It would have been difficult to freeze these sites with direct pour of liquid nitrogen due to the relatively large size of the funnels.

### PEARLS AND PITFALLS

**Surgery**
- Mobilization of the neurovascular bundle and surrounding soft tissues
- Adequately large cortical window
- Meticulous curettage followed by high-speed burr
- Soft tissue protection and warming throughout cryoablation
- Reconstruction of the tumor cavity with cemented hardware and of the subchondral surface with autologous bone graft

**Postoperative**
- Protected weight bearing postoperatively

### POSTOPERATIVE CARE
- Routine perioperative prophylactic antibiotics are administered for 3 to 5 days. Patients with lesions of the lower extremities are kept non-weight bearing for 6 weeks. Plain radiographs are then obtained to rule out fracture and establish bone graft incorporation. Gradual weight bearing is allowed if healing has progressed satisfactorily.

### OUTCOMES
- By far the most extensive experience with cryoablation has involved giant cell tumor of bone, a benign–aggressive primary bone tumor. Two thirds of these lesions occur in the third or fourth decades of life, and, in most cases, they are located in the metaphyseal-epiphyseal region of long bones around the articular cartilage. Because wide excision of such tumors would cause major loss of function due to their proximity to the joint, it had been common practice to opt for intrallesional procedures, but the rate of local recurrence, mainly after curettage, was unacceptably high (ie, 40%-55%).
- The use of cryoablation with liquid nitrogen, as an adjuvant to curettage and high-speed burr drilling, substantially lowered the recurrence rate. Malawer et al reported a 2.3% recurrence rate among 86 patients treated primarily with cryoablation. They reported good-to-excellent functional outcome in 92% percent of the patients (FIG 1).
functions were reported with other benign–aggressive and malignant tumors.3,4,9,14,23–25,28,30,31,34,35,37,38,40,44–46,49

**COMPLICATIONS**

- Gage et al13 observed that cryoablation is a double-edged sword, ie, that it induces tumor necrosis with similar injury to the surrounding normal tissues. This potential drawback initially was underestimated by surgeons who pioneered the application of this technique in clinical practice. Inadequate protection of soft tissues, lack of mechanical fixation, and failure to use perioperative antibiotics resulted in unacceptably high rates of fractures, soft tissue injury, infections, and neurapraxias.32

- Those complications gave cryoablation its bad reputation and motivated surgeons to refine the surgical technique to include concomitant soft tissue mobilization and protection, stable reconstruction with cemented internal fixation devices, and the use of perioperative antibiotics. As a result, the same authors reported a later series of patients with a significantly reduced rate of those complications.39,52

- Postoperative fractures have been a devastating complication of cryoablation (FIG 2A,B). They were considered pathological because they occurred through a mechanically weakened bone and following a minor trauma.4,20,27,33,39 These fractures healed slowly (over a period of 3 to 9 months) and were associated with a significant loss of function. Lack of stable fixation and early weight bearing were shown to be the important factors leading to these fractures, and the treatment protocol was changed accordingly: the consensus was that cryoablation must be followed by stable reconstruction that includes internal fixation reinforced with PMMA and a strict rehabilitation protocol of gradual weight bearing.27,32,39 This regimen resulted in a minimal rate of postoperative fractures, as reported in series published from the 1990s to date.4,24,27,44,46,49,50

- When such postoperative fractures do occur, surgical intervention usually is not required. The fracture lines invariably are along the internal fixation device, so the fracture is not significantly displaced, and immobilization and avoidance of weight bearing usually are sufficient for treatment. Infections and flap necrosis also have become rare complications due to mobilization and protection of soft tissues prior to freezing and the use of perioperative antibiotics.

- Mobilization of the neurovascular bundle and surrounding soft tissues away from the tumor site, as well as the use of perioperative antibiotics, has led to low rates of infections, thermal injuries, and nerve palsies (FIG 2C). When the latter do occur, the neurologic damage usually is transient and heals spontaneously. Cryoablation also was shown to be associated with minimal damage to the adjacent articular cartilage, with degenerative changes reported in less than 3% of cases in a large series of patients.27

**FIG 1** • Full flexion of the knee in a 54-year-old man 3 months following cryoablation of a chondrosarcoma of the lateral femoral condyle. It would have been difficult to achieve such a range and muscle strength after the resection of the distal femur that otherwise would have been offered to this patient.

**FIG 2** • A. Plain radiograph showing pathological fracture of the proximal tibia following cryoablation and on weight bearing. Reconstruction following cryoablation in that patient consisted of autologous bone graft only. B. The wide collapse and destruction of the articular surface made resection of the proximal tibia and reconstruction with endoprosthesis inevitable. C. Thermal injury to the leg due to spillage of liquid nitrogen. The soft tissues apparently were not well protected in this patient during freezing. This complication is rare when adequate padding and warming with saline are carried out. It is even more uncommon when using the closed argon-based system, which does not involve any poured fluid whatsoever.
Cryoablation achieves best local tumor control when applied for microscopic disease and in tumors that have not caused major cortical destruction and invasion into the surrounding soft tissues. Any compromise of either of these criteria ultimately may result in local tumor recurrence. Better case selection, adequate curettage, and meticulous burr-drilling have led to a drop in local recurrence rates, to less than 5% in most series. A second cryoablative procedure is curative in most local recurrences.

Venous gas embolism is a rare complication of open cryoablation with liquid nitrogen, having been reported in only 4 cases. Liquid nitrogen rapidly produces nitrogen bubbles (N2) at room temperature. Although most of the gas exits into the atmosphere through the surgical wound, a considerable amount nonetheless is pushed into the pulmonary circulation under the influence of the pressure caused by boiling of liquid nitrogen in the bony cavity, and exhaled. It usually manifests intraoperatively with decreased O2 saturation level and end-tidal CO2, associated with a drop in blood pressure and a rise in the heart rate. These emboli usually resolve completely with early detection, discontinuation of nitrous oxide administration, and support with oxygen.

**REFERENCES**


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