The role and biology of cryosurgery in the treatment of bone tumors

A review

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The application of liquid nitrogen as a local adjuvant to curettage in the treatment of bone tumors was introduced three decades ago. This technique, termed cryosurgery, was shown to achieve excellent local control in a variety of benign-aggressive and malignant bone tumors. However, early reports showed that cryosurgery was associated with a significant injury to the adjacent rim of bone and soft-tissue, resulting in high rates of fractures and infections. These results reflected an initial failure to appreciate the potentially destructive effects of liquid nitrogen and establish appropriate guidelines for its use. We review the biological effect of cryosurgery on bone, surgical technique, and current indications for its use.

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Cryosurgery is the therapeutic use of cold to induce tissue necrosis with ablative intent. The first report on the use of local freezing as a treatment modality is attributed to Dr. James Arnott (1850), who described the direct application of a salt-ice mixture to various skin lesions. He noticed a marked anesthetic and hemostatic effect and advocated its use, mostly as a palliative treatment, in a large variety of diseases, ranging from headache to advanced carcinoma of the cervix and fungating breast cancer. For almost a century, cryosurgery was practiced by a handful of surgeons in the fields of neurosurgery, gynecology, urology, and ophthalmology. Solid carbon dioxide, cold air blast, and liquid nitrogen (LN) were used as cryogenic agents to treat various benign and malignant lesions and achieved good results in local tumor control and residual scarring (Holden 1975).

Cooper (1962) described a cryotherapy unit in which LN was circulated through a hollow metal probe. This equipment made it possible, by means of interrupting the flow of liquid nitrogen, to control the temperature of the tip of the probe within the range of room temperature to –197 °C. Because this was a totally closed system, one could apply the cold to any point in the body accessible to the probe. The first clinical application of this technique, termed a "closed system", was in the treatment of Parkinson's disease (Holden 1975). Gage et al. (1966) treated malignant soft-tissue lesions of the oral cavity with cryotherapy and observed that the adjacent frozen bone eventually healed. In their classic study, Gage et al. used a closed system of latex tubes with LN circulating in coils surrounding the diaphyses of dog femora. LN was used as a cryogenic agent because of its ability to induce rapid freezing of large lesions. The procedure was demonstrated to induce bone necrosis, followed by slow healing and new bone formation (Gage et al. 1966, Schargus et al. 1975, Kuylenstierna et al. 1981).

The first use of cryosurgery in conjunction with orthopedic surgery is attributed to Marcove and Miller (1969), who described an "open system" that entailed pouring LN directly into a tumor cavity. They treated a 48-year-old male with a painful metastatic lung carcinoma in the proximal humerus that was resistant to radiation therapy. The patient experienced complete relief of his pain following treatment (Marcove and Miller 1969). Liq-

uid nitrogen was shown to achieve local tumor control with minimal bone and function loss and cryosurgery was soon practiced in conjunction with surgery for a large variety of bone tumors (Marcove and Miller 1969, Marcove et al. 1977a,b, 1978).

Despite its proven benefits, liquid nitrogen is a powerful local adjuvant which, when not used with caution, may cause substantial injury to the adjacent rim of bone, cartilage, and soft tissues and result in secondary fracture, skin necrosis, infection, and temporary neuropraxia (Marcove and Miller 1969, Marcove et al. 1973, 1977a). The early series had high complication rates that reflected an initial failure to appreciate these potentially destructive effects and establish an appropriate surgical technique. The high complication rate gave this treatment a poor reputation, and during the last three decades, only a few orthopedic surgeons used cryosurgery routinely. Nonetheless, their experience helped to define the precautions and indication for its use. Cryosurgery was found to be effective for treating liver metastases (Weaver et al. 1995, Korpan 1997) and genitourinary malignancies (Creasman et al. 1984, Miller et al. 1996, Wong et al. 1997). In the field of orthopedic oncology, cryosurgery was shown to be a curative treatment for benign-aggressive and low-grade malignant bone tumors. Cryosurgery could also achieve local tumor control and symptomatic relief in metastatic bone disease (Malawer et al. 1991, 1999, Marcove et al. 1994, 1995, Schreuder et al. 1997a, c, 1998). In this article, we review the biological effect of cryosurgery on bone, its advantages and limitations, surgical technique, and current indications for its use.

Biology of cryosurgery

Liquid nitrogen, stored at –197 °C, is an effective cryogenic agent that can be used for either tissue preservation or destruction. A slow freeze and quick thaw allow tissue preservation, a quick freeze and slow thaw lead to its destruction (Gill et al. 1968). Cryosurgery utilizing LN is effective in the treatment of bone tumors, because bone necrosis occurs at temperatures below –21 °C (Gage et al. 1966, Schreuder et al. 1997b). The formation of intracellular ice crystals and membrane disruption are considered the main mechanisms of LN-induced cellular necrosis. Other mechanisms of cytotoxicity include electrolyte changes, denaturation of cellular proteins, and microvascular failure (Karow and Webb 1965, Mazur 1970, McGann et al. 1975, Miller and Mazur 1976, Harris and Griffiths 1977, Malawer et al. 1988). During cryotherapy, the rapid freeze causes intracellular ice crystals to form. As the temperature rises during thawing, these crystals coalesce and mechanically disrupt the cell membrane, causing cell-death. Repetitive freeze-thaw cycles increase the amount of necrosis. Such changes are explained by increased thermal conductivity in the frozen lesion that results from an alteration in the basic structure of the tissue (Gill et al. 1968) and are proportional to the duration of exposure to LN (Gage et al. 1966).

Histological evaluation of the cortex, immediately following cryosurgery, shows minimal changes. The extent of cortical injury does not become appearent until a week after application of LN; by this time, periosteum over the previously frozen cortex has disappeared, and the denuded bone appears dull white. The most dramatic effect of LN application may be seen in the bone marrow and is characterized by extensive necrosis, with minimal inflammation and subsequent liquefaction with progressive fibrosis. Large, thickened thrombosed vessels are occasionally seen (Gage et al. 1966, Schargus et al. 1975, Kuylenstierna et al. 1980, Malawer et al. 1988). Bone repair, beginning in the periphery of the bone cavity, occurs slowly and is first evident at 2 months. Only after 6 months is the new bone formation sufficient to prevent pathologic fracture. The histological features after repeated freeze-thaw cycles are almost identical with those described for a single episode of freezing (Gage et al. 1966).

Malawer et al. (1988) demonstrated a 7- to 12-mm rim of bone necrosis, with no effect on articular cartilage, when liquid nitrogen was utilized in a dog model (Figure 1). Marcove et al. (1978) stated that three freeze-and-thaw cycles produce tumor cell death up to 2 cm from the cavity margin. This extent of bone destruction makes cryosurgery, which is by definition an intralesional surgical modality, as effective as a wide resection in the

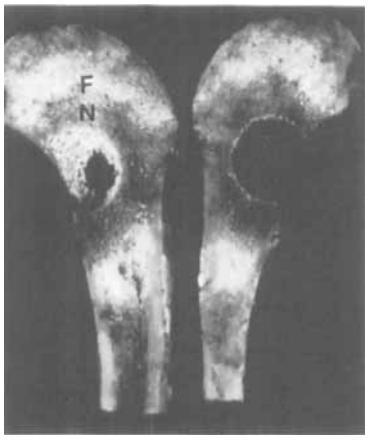

Figure 1. Canine distal femur treated with liquid nitrogen. Tetracycline fluorescence demonstrates a circumferential rim of no fluorescence around the cavity, which corresponds to the extent of bone necrosis (N), and an adjacent rim of fluorescence (F), which corresponds to an area of attempted bone repair.

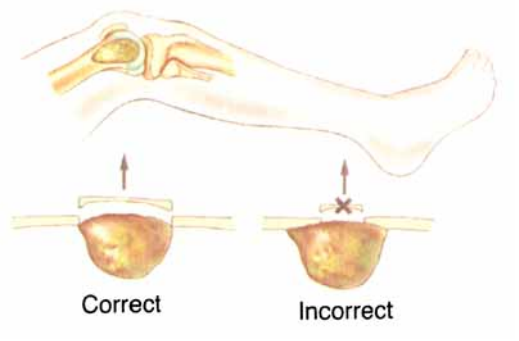

Figure 2. A large cortical window, the size of the largest diameter of the lesion, is essential for adequate exposure. A smaller window is not sufficient for complete curettage and burr drilling of the tumor.

treatment of benign-aggressive, low-grade primary bone sarcomas, or metastatic lesions (Marcove et al. 1977a, b, Schreuder et al. 1998, Malawer et al. 1999). High-grade bone sarcomas, on the other hand, usually have a significant soft-tissue extension that is not affected by LN, unless poured directly on it. This is not recommended, due to the fear of damage to the surrounding muscles and neurovascular bundle. Articular cartilage seems to be resistant to cryotherapy and remains intact, even when freezing extends to the subchondral bone or crosses the joint (Malawer et al. 1988, Aboulafia et al. 1994).

Surgical technique

Although a simple procedure, cryosurgery can cause substantial morbidity if performed inappropriately. An effective and safe procedure must follow these consecutive steps: 1) adequate exposure of the tumor cavity, (2) meticulous curettage and burr drilling, (3) soft-tissue mobilization and protection prior to introduction of LN to the tumor cavity, (4) internal fixation of the cavity after cryotherapy and (5) protection of the operated bone throughout the healing period.

Exposure

When possible, a pneumatic tourniquet is used to reduce local bleeding and prevent blood from acting as a heat sink and a thermal barrier for the cryotherapy. Benign-aggressive, low-grade primary bone sarcomas, and metastatic tumors rarely invade the articular cartilage and an extracapsular approach is therefore possible in most cases. The joint cavity should not be opened, to avoid contamination by tumor cells and the risk of injury to the cartilage following direct exposure to liquid nitrogen. After exposure of the involved bone and soft tissues, a cortical window the size of the longest longitudinal dimension of the tumor is made. To minimize additional bone loss, the tumor is approached through the retained thinned or destroyed cortex. A large cortical window is essential to expose the entire tumor and avoid inadequate curettage. The window must be elliptical, and its axis must be parallel to the long axis of bone, to reduce the stress-rising effect (Figure 2).

Curettage

All gross tumor is removed with hand curettes. After the neoplastic tissue has been curetted away from the inner wall of the lesion, the reactive wall reveals an irregular contour. This irregularity makes it virtually impossible to remove all the tissue from the inner reactive shell with a curette. Therefore, curettage is followed by high-speed burr drilling (Figure 3).

Cryosurgery

Before introduction of the liquid nitrogen, bony perforations are identified and sealed, and the surrounding skin, soft tissues, and neurovascular

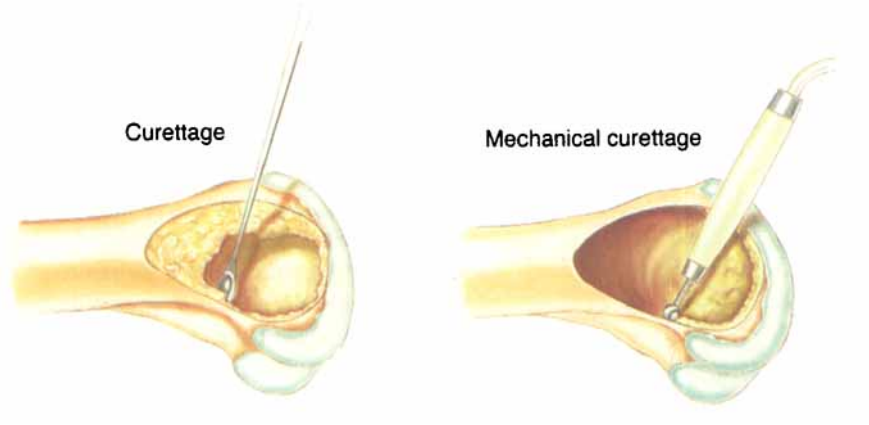

Figure 3. Curettage of the tumor cavity is followed by meticulous burr drilling until no tumor matrix is further seen

bundle are protected by mobilization and shielding with Gelfoam®. Large skin flaps are retracted to protect them from possible spillage of the liquid nitrogen.

Liquid nitrogen can be applied to a bony cavity by direct pouring (open system) or by perfusing it through metal probes (closed system) (Cooper 1962, Holden 1975, Jacobs and Clemency 1985) (Figure 4). Cryosurgery is not effective unless a close contact is achieved between the LN and the outermost layer of the tumor cavity. Therefore, size and configuration of the tumoral cavity determinate the chosen technique. Most bone lesions have a large, irregular inner wall, and use of the open system makes it possible to spread homogeneously the LN throughout the cavity. Liquid nitrogen spray is an "open system", used for unique anatomic locations, in which pouring of liquid nitrogen is not technically feasible (for example, deep-seated pelvic lesions).

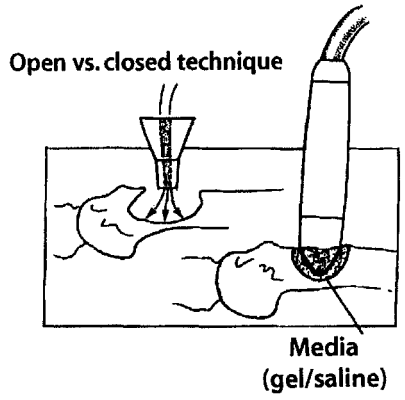

Figure 4. Metal probes used for the closed system of cryosurgery, which is most suitable for Small and regular cavities. Large and irregular cavities are best treated with direct pour of liquid nitrogen.

The closed system, on the other hand, can be effectively used in small, regular cavities, such as those remaining after curettage of a small lesion in the digits or the distal radius.

Using the open system, LN is poured through a stainless-steel funnel into the tumor cavity. Care is taken to fill the entire cavity. The Gelfoam® blocks immediately freeze, forming a tight seal around the funnel. Thermocouples are used to monitor the freezing effect in the cavity, cavity wall, and adjacent soft tissue, as well as in the area 1–2 cm from the periphery of the cavity. The surrounding soft tissues are continuously irrigated with warm saline solution to reduce the possibility of thermal injury (Figure 5). In each cycle, liquid nitrogen is left in the cavity until it has completely evaporated. Each cycle lasts 1–2 minutes and is proportional to the volume of poured liquid nitrogen. Spontaneous thaw is then allowed to occur over a period of 3–5 minutes. Once the temperature of the cavity rises above 0 °C, the cycle is considered completed. Two freeze-thaw cycles are used, at the end of each of which the cavity is irrigated with saline solution.

Reconstruction

Reconstruction is performed using polymethylmethacrylate (PMMA), internal fixation, and subchondral bone graft (Figures 6 and 7). The subchondral surface is reconstructed with bone graft

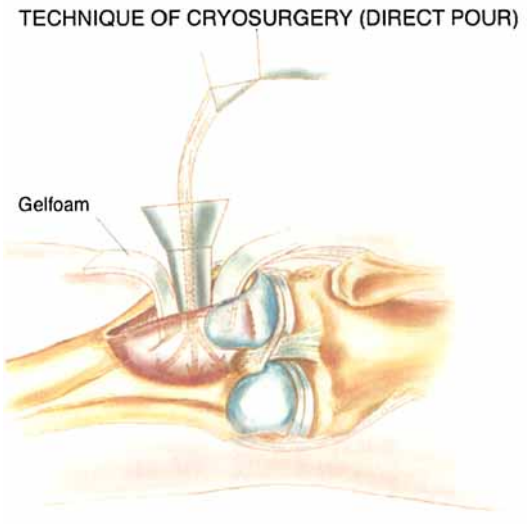

Figure 5. Liquid nitrogen is poured through a stainless steel funnel. Temperature within the cavity, as well as in the surrounding bone and soft tissues, is monitored with thermocouples. Soft tissues are immobilized, protected with Gelfoam®, and irrigated continuously with warm saline solution

prior to cementation. Internal fixation is strongly recommended, as indicated by recently reported long-term follow-up results in a large series of patients with giant cell tumor of bone, who were treated with cryosurgery (Malawer et al. 1999). In that series, fractures occurred only when internal fixation was not used as part of reconstruction. The combination of PMMA and internal fixation provides immediate stability and structural support for large defects and allows early rehabilitation of the adjacent joint.

Postoperative management

Routine perioperative prophylactic antibiotics are administered for 3–5 days. The wound is examined on the third day after surgery. If the skin is intact, passive and active motion of the adjacent joint are practiced. Patients with lesions of the lower extremities are kept partial-weight bearing for 6 weeks. Plain radiography is then performed to rule out fracture and establish bone graft incorporation. If healing progresses satisfactorily, weight bearing is allowed. Patients are instructed to avoid high-impact activities for 6 additional months.

Complications

Exposure of normal bone and soft tissues (skin, muscles, nerves, and blood vessels) to the freezing effect of LN can result in substantial morbidity. Early studies of the use of cryosurgery in the treatment of bone tumors reported high complication rates, mostly pathological fractures and infection (Table 1). Many of these early investigators did not recognize the importance of soft tissue protection, use of PMMA and internal fixation for reconstruction, and protecting the operated extremity pending complete healing. Gage et al. (1966) performed cryosurgery on 34 dog femora and docu-

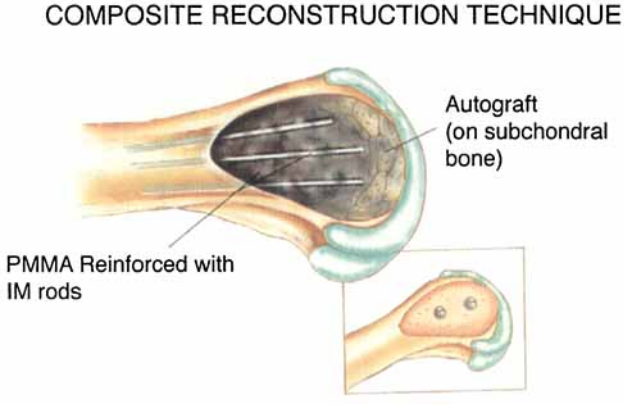

Figure 6. Reconstruction of the tumor cavity, using subchondral bone graft, followed by intramedullary hardware and polymethylmethacrylate.

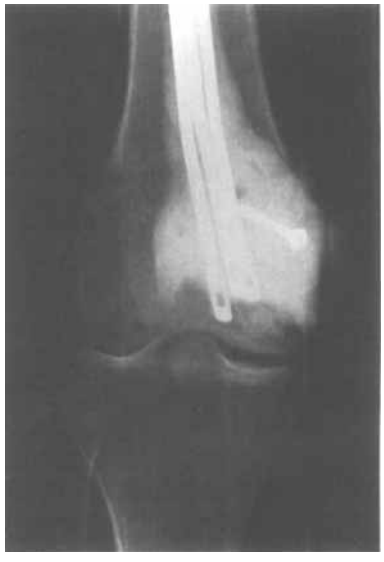

Figure 7. Plain radiograph of the distal femur following cryosurgery and reconstruction.

Table 1. Summary of literature review on complication rates following cryosurgery

Author (year)	Cases	Complications					
		Fracture	Infection	Skin necrosis	Joint degeneration	Nerve palsy	Other
Marcove 1969	57	4	–	6	–	–	–
Marcove 1973	52	13	8	–	2	4	–
Marcove 1977	18	7	–	–	3	4	–
Jacobs 1985	12	6	–	–	–	–	–
Malawer 1991	25	2	–	1	–	–	Synovial fistula (1)
Aboulafia 1994	9	–	–	–	–	–	–
Marcove 1994	7	–	2	–	–	–	Rectal fistula (1)
Marcove 1995	51	5	–	–	–	1	–
Schreuder 1997c	26	1	2	–	–	1	–
Schreuder 1998	26	2	1	–	–	–	Venous gas embolism (1)
Malawer 1999	102	6	–	3	2	1	–

mented a pathologic fracture in 10 femora when activity was not restricted and the operated bone was not protected. Marcove et al. (1978) practiced cryosurgery prior to the use of PMMA, combined with onlay bone graft and/or internal fixation. He made only a minimal attempt to reconstruct the bone defect remaining after curettage and cryosurgery and reported a postoperative fracture rate of 25% in his early series. Malawer et al. (1999) reported 6% pathologic fractures following cryosurgery among 102 patients, treated with cryosurgery for giant cell tumor of bone. As mentioned, all these fractures occurred when internal fixation was not used for reconstruction.

Prophylactic antibiotics, wide exposure, and adequate mobilization of skin flaps and adjacent neurovascular bundle, along with continuous irrigation of tissues with warm saline solution, reduce the incidence of skin necrosis. Malawer et al. (1999), who used this technique, reported no cases of infection and only 3/102 cases of partial skin necrosis. The latter were due to contact with leaking liquid nitrogen and were satisfactorily managed by nonsurgical treatment. Nerve palsy after exposure to LN occurs in less than 1% of patients and is usually transient (Marcove et al. 1995, Schreuder et al. 1997c, Malawer et al. 1999).

Clinical application

By far the most extensive orthopedic surgical experience with cryosurgery has involved giant cell tumor (GCT) of bone, a benign aggressive primary bone tumor (Table 2). 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 (Huvos 1991). Because wide excision of such tumors would cause major loss of function, due to their proximity to the joint, intralesional procedures have been common. However, the rate of local recurrence, mainly after curettage, has been unacceptably high—i.e., 40%–55% (Johnson and Dahlin 1959, Goldenberg et al. 1970, McDonald et al. 1986, Campanacci et al. 1987). The introduction of liquid nitrogen, as an adjuvant to meticulous curettage and burr drilling, substantially lowered the recurrence rate; Malawer et al. (1999) used cryosurgery to treat GCT of bone and reported a 2.3% recurrence rate among patients treated primarily with cryosurgery.

Marcove and Miller (1969) used cryosurgery to treat a variety of benign and malignant bone tumors and concluded that it should be reserved for benign-aggressive bone tumors. Surgical treatment of high-grade primary bone sarcoma necessitates wide excision of the tumor with its soft-tissue component (Petersson et al. 1987); any violation of the tumor margins is associated with a high risk of local tumor recurrence. Cryosurgery is not appropriate for high-grade primary bone sarcomas since it is an intraosseous procedure with minimal effect on the soft-tissue component of the tumor. Bone tumors that have little, if any, soft-tissue component, such as low-grade, unicompartmental

Table 2. Summary of literature review on bone tumors treated with cryosurgery

Tumor type	Author
Benign aggressive lesions	
Giant cell tumor	Aboulafia 1994, Jacobs 1985, Malawer 1991, 1999, Marcove 1969, 1973, 1978, 1994,
Enchondroma	Schreuder 1998
Chondroblastoma	Schreuder 1998
Unicameral bone cyst	Schreuder 1997a
Aneurysmal bone cyst	Marcove 1969, 1995, Oeseburg, 1978, Schreuder 1997c
Fibrous dysplasia	Marcove 1969
Hemangioma of bone	Marcove 1969
Sacral chordoma	Marcove 1969, Vries 1986
Eosinophilic granuloma	Marcove 1969
Metastatic lesions	
Carcinoma of lung	Marcove 1969
Carcinoma of breast	Marcove 1969
Carcinoma of prostate	Marcove 1969
Hypernephroma	Marcove 1969, 1977a
Carcinoma of bladder	Marcove 1969
Soft-tissue sarcoma	Marcove 1969
Adenocarcinoma of uterus	Marcove 1969
Primary bone sarcomas	
Osteosarcoma	Marcove 1969, 1984
Chondrosarcoma	Marcove 1969, 1977b, Schreuder 1998
Other	
Multiple myeloma	Marcove 1969

chondrosarcomas and metastatic tumors of bone, can be treated with cryosurgery (Marcove and Miller 1969, Marcove et al. 1977, Schreuder et al. 1998).

Summary

Cryosurgery is an effective adjuvant to curettage for various benign and malignant bone tumors. It is a curative procedure in the treatment of benign aggressive bone lesions, and of low-grade primary bone sarcomas of bone, and can achieve local control in metastatic bone disease. The previously reported high rates of fracture and infection can be avoided by careful attention to surgical details. Adequate exposure, meticulous curettage and burr drilling, soft-tissue mobilization and protection, and routine use of internal fixation with PMMA for reconstruction are essential.

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