Fracture Risk With Pressurized-Spray Cryosurgery

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Abstract

Forty-two patients treated with curettage, burring, direct pressurized cryotherapy, and bone grafting or cementation were retrospectively reviewed. There were no pathologic fractures in this study group, compared with a 17% fracture rate in recent studies using the "direct pour" technique. Direct pressurized cryotherapy was used in 3 separate freezing cycles in each case. This approach may significantly reduce the risk for fracture compared with historical controls using the direct-pour technique.

Cryosurgery involves use of liquid nitrogen as an adjuvant to induce tissue necrosis and destruction of tumor cells. In 1969, Marcove and Miller[1] used liquid nitrogen in the surgical management of a metastatic carcinoma of the proximal humerus, and later for treatment of a variety of benign and low-grade malignant bone tumors. They advocated use of the "direct pour" liquid nitrogen cryotherapy method to avoid more extensive resection and reconstruction and to decrease local recurrence after surgical intervention.[2] The direct-pour technique begins with exposing the target area and performing curettage to remove gross tumor. After obtaining hemostasis and protecting the surrounding tissues, the surgeon then pours liquid nitrogen directly into the curetted cavity. Adequate contact time is allowed, and the process is repeated several times with subsequent temperatures below –20°C at the bone interface. The freezing effect destroys adjacent cells in the walls of the cavity and extends the margin of tumor cell removal.[2] Gage and colleagues[3] and Schreuder and colleagues[4] found that cellular apoptosis is caused by bone necrosis secondary to formation of ice crystals and membrane disruption occurring at temperatures below –21°C.

When cryosurgery was first used, it proved to be an effective adjuvant in the treatment of bone tumors. In early studies involving liquid nitrogen adjuvant therapy, Marcove[1,2] reported local recurrence rates of 4% to 10%. Subsequent studies confirmed no adverse increase in recurrence rates over wide resection in benign-aggressive, low-grade primary bone sarcomas, and metastatic lesions.[4-8] However, cryosurgery is not a benign adjuvant in the treatment of bone tumors. As use of cryosurgery has become prevalent, investigators have noted several secondary posttreatment complications: infection, nerve palsy, soft-tissue damage, and pathologic fracture.[2,6,9-12]

Of particular interest is the incidence of pathologic fracture, which early on was as high as 25% to 50%—a factor that limited dissemination of the technique.[2,13] It was noted that, as cryosurgery increases the extent of tumor removal, it also extends the area of impaired bone healing.[5,9] Impaired bone healing leaves patients susceptible to pathologic fracture. However, Malawer and colleagues[5] showed that the fracture rate with use of the "open pour" technique can be reduced to 6% by adding prophylactic internal fixation. As surgeons began routinely using meticulous bone reconstruction with internal fixation, polymethylmethacrylate, and bone grafting to support the anatomical defect, the first significant reduction in the pathologic fracture rate was noted. In more recent reviews of surgical outcomes, the rate of postoperative pathologic fracture with direct-pour cryosurgery was estimated to be between 6% and 17%.[5,14]

We believe that the next large reduction in pathologic fracture rates with liquid nitrogen adjuvant therapy will come with changes in application methods. An early concern was the limited ability to control application of liquid nitrogen, which correlated to increased risk for complications.[2,15] More recently, a "pressurized spray" cryosurgical technique evolved from the direct-pour technique. The surgeon prepares the target field in similar fashion but uses a spray canister to apply the liquid nitrogen. Pressurized spray allows for even application, rapid evaporation, and avoidance of pooling.[11] Again, cryogenic freezing is repeated several times and

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Figure 1. Cryogun liquid nitrogen applicator (Brymill, Ellington, Connecticut) used in these procedures.

is followed by the same reconstruction options that are available for direct pour. Early studies demonstrated that the pressurized-spray technique may be equally effective in controlling tumors and minimizes the secondary complications, including pathologic fracture. Dabak and colleagues[16] reported no pathologic fractures in the early results of 17 patients. Veth and colleagues[12] found that the pressurized-spray technique is at least equally effective in terms of preventing recurrence.

Our goal in the present study was to address what we believe may be the next logical step in reducing pathologic fractures: using pressurized-spray cryosurgery (instead of direct-pour cryosurgery) as an adjuvant in the treatment of bone tumors.

Materials and Methods

Initially, we identified 57 patients treated with curettage and cryosurgery by the study's senior author (J.L.M.) at Ohio State University between 2002 and 2006. Further inclusion criteria were diagnosis of benign or low-grade malignant bone tumor and postoperative follow-up of 6 months or longer. One patient was excluded because of a pathologic diagnosis of chronic osteomyelitis, and another because of amorphous foreign material. Thirteen other patients did not meet the follow-up minimum of 6 months. The remaining 42 patients were included in the analysis. All patients were initially evaluated in the outpatient setting, and radiographs were taken for surgical planning. When clinically indicated, advanced radiographic imaging (eg, computed tomography, magnetic resonance imaging) was performed to characterize the tumor more accurately.

In each case, a cortical window was opened, curettage was performed, and mechanical burring was used to complete the tumor extirpation. Then, the pressurized-spray Cryogun (Brymill, Ellington, Connecticut) (Figure 1) was used to apply liquid nitrogen to the tumor bed, which was frozen until ice crystals were directly visible on all surfaces. The bed was then allowed to thaw slowly (saline was introduced to assist with thawing). Each patient underwent 3 freeze–thaw cycles (Figure 2). Biplanar fluoroscopy was used to document the extent

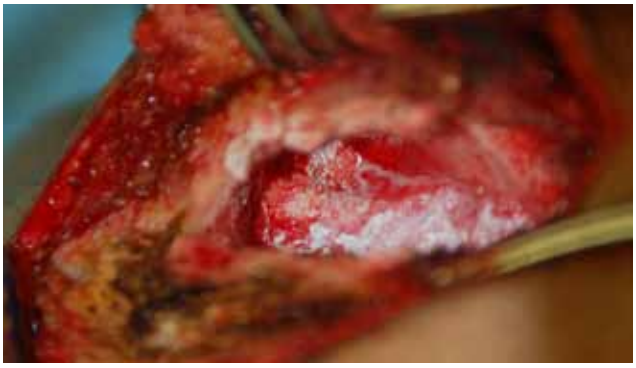

Figure 2. Intraoperative photograph of curettaged and burred tumor cavity after cycle of direct pressurized-spray liquid nitrogen cryotherapy.

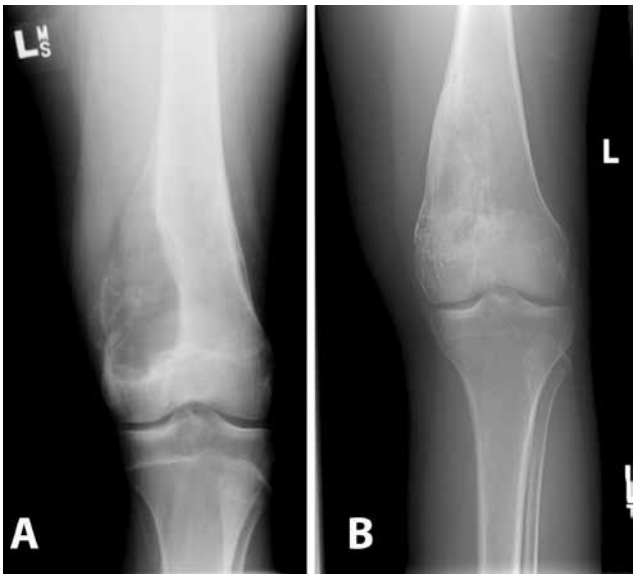

Figure 3. Aneurysmal bone cyst of distal femur before (A) and after (B) curettage, cryosurgery, and bone grafting.

of curettage. Adjuvant cryosurgery was followed by filling with bone graft or cementation and, in some cases, reinforcement with prophylactic internal fixation. Finally, biplanar fluoroscopy was used to document the reconstruction, the proper placement of the hardware, and the replacement of the bone window.

Radiographs were obtained after surgery. Toe-touch weight-bearing was used for 6 to 12 weeks, according to lesion size and location. Weight-bearing and activity were advanced with demonstration of acceptable radiographic evidence of bone healing. Patients were clinically followed up at 2, 6, and 12 weeks; then at 3-month intervals for 2 years; then at 6-month intervals for year 3; and then yearly thereafter. Radiographs were taken at follow-up visits to monitor for recurrence, pathologic fractures, hardware position, and bone graft incorporation.

Results

Mean age of the 42 patients (31 women, 11 men) was 39 years (range, 15-80 years). Mean clinical and radiographic

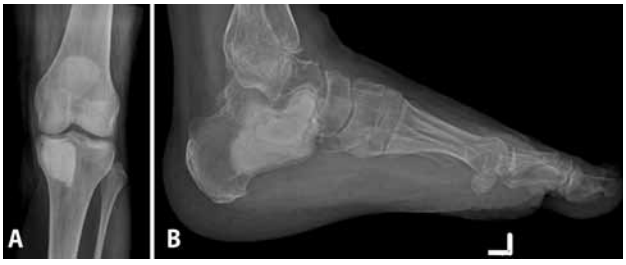

Figure 4. Radiographs of giant cell tumor of medial tibia (A) and calcaneus (B) after curettage, cryosurgery, and cementation in different patients.

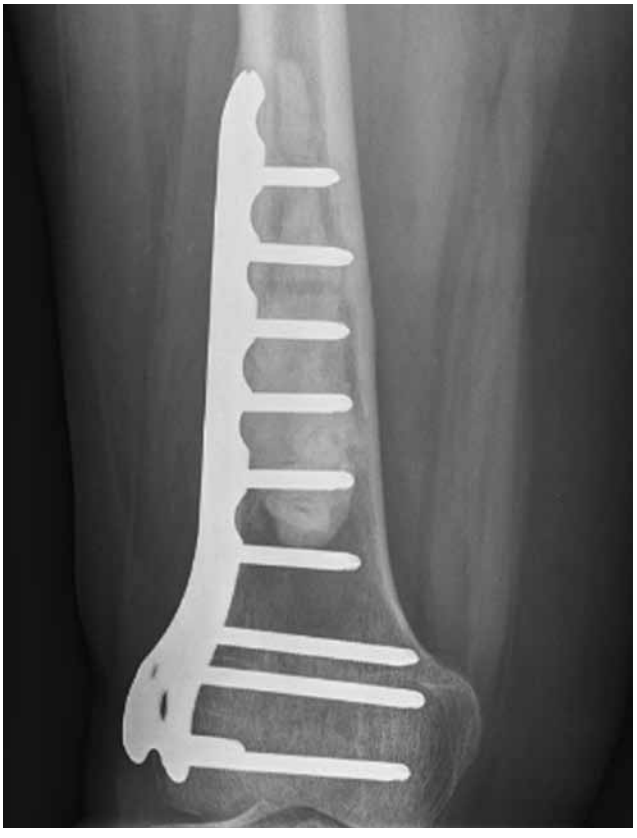

Figure 5. Radiograph after curettage, cryosurgery, cementation, and prophylactic internal fixation.

follow-up was 22 months (range, 6-40 months). With respect to histologic diagnoses, there were 29 low-grade cartilage tumors (including enchondroma and low-grade chondrosarcoma), 8 giant cell tumors (GCTs) of bone, 4 aneurysmal bone cysts, and 1 hemangioendothelioma. Most of the tumors were located on the major long bones (15 femoral, 11 humeral, 6 tibial, 4 fibular, 1 radial). The other 5 tumors were located on the metatarsal/phalanges (3), the supra-acetabular ilium (1), and the calcaneus (1).

After cryosurgery, 27 patients underwent bone grafting alone, 5 underwent bone grafting and prophylactic internal fixation (Figures 3–5), 4 underwent cementation alone, 5 underwent cementation and prophylactic internal fixation, and 1 underwent bone grafting and cementation. Five (12%) of the 42 patients had a local recurrence.

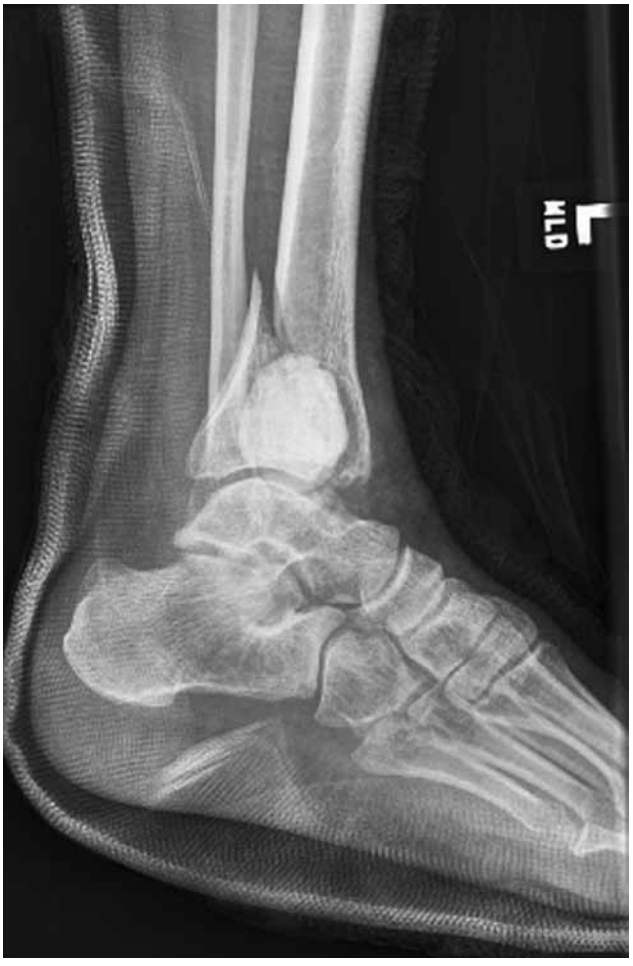

Figure 6. Radiograph of distal tibia pilon fracture after motor vehicle accident that involved patient who initially presented with giant cell tumor of distal tibia and was treated with curettage, cryosurgery, and cementation.

Two patients with GCT of bone and 1 with aneurysmal bone cyst underwent a second round of cryosurgery and repeat cementation. These 3 patients were followed for 28, 14, and 6 months, respectively, without evidence of recurrence. Two other patients with local recurrence required more aggressive, surgical treatment. One of these patients had a recurrent low-grade chondrosarcoma and underwent resection and hemiarthroplasty; the other patient's tumor, diagnosed initially as a low-grade cartilage tumor, underwent dedifferentiation to a high-grade chondrosarcoma in the first metatarsal, and below-knee amputation was required.

In this cohort of 42 patients treated with direct-spray cryosurgery, there were no pathologic fractures. All patients were followed regularly with outpatient visits and radiographs to document healing and rule out recurrence or fracture.

It is important to note, however, that 2 patients subsequently sustained fractures of the surgical site in accidents that involved significant trauma. One of these patients underwent curettage, cryosurgery, and cementation for a distal tibial GCT, recovered uneventfully, and

was released to work at 4 weeks. At 6 months, he was in a motor vehicle collision and sustained a distal tibia pilon fracture that required open reduction and internal fixation (Figure 6). He recovered uneventfully and underwent a second procedure, for hardware removal, almost 4 months after the first surgery. At the first visit after hardware removal, he reported improved function. He was noted to have stable fracture alignment and was released to work but later was lost to follow-up.

The other patient underwent curettage, cryosurgery, and internal fixation for a painful midshaft femoral enchondroma. At 3 months, she was recovering well and had good range of motion, no evidence of fracture, and none of the preoperative knee pain. One month later, she presented after taking a painful step and falling. At this visit, she had full range of motion and no fracture, recurrence, or change in hardware position on plain radiographs. At 6-month follow-up however, plain radiographs showed a healing fracture callus, likely secondary to a nondisplaced fracture that had not been evident at 4 months. At 9 months, the fracture was healed and the patient continued to do well. She was last seen 14 months after surgery.

Our study group had other complications, including peri-incisional numbness and nerve palsies, commonly associated with cryosurgery. Three patients reported of ongoing peri-incisional numbness. Two of these patients first reported the numbness at 2-month follow-up; return of near normal sensation was documented at 5 and 9 months, respectively. The third patient first reported altered sensation around the incision at 15-month follow-up; sensation was back to normal by 22-month follow-up. There was no skin necrosis or infection in our study group. One patient had an asymptomatic heterotrophic ossification noted radiographically.

Discussion

Since direct-pour cryosurgery was introduced in 1969, liquid nitrogen has become a valuable adjuvant in the treatment of bone tumors. Still, it has its complications, including postoperative pathologic fracture.

Phenol, argon beam coagulation, and hydrogen peroxide also have been proposed as adjuvant treatments to decrease local recurrence in benign aggressive bone tumors. Phenol acts as a direct cytotoxic agent by coagulating protein. Capanna and colleagues[17] found a decrease in the local recurrence rate, from 41% to 7%, with application of phenol in benign bone tumors. The main risks are toxicity to surrounding soft tissues, possibly including nearby neurovascular structures, and delayed wound healing. Bone necrosis also likely occurs but has not been studied.

Cummings and colleagues,[18] who recently studied argon beam coagulation as adjuvant treatment for aneurysmal bone cysts, found no local recurrences with its use and 4 local recurrences in its absence. As argon beam coagulation has been in use for a relatively short time, its potential complications are not fully elucidated. In theory, it may have the same potential complications that liquid nitrogen has. Depth of necrosis has not been studied. Nerve palsy, infection, and soft-tissue injury are certainly possible risks.

The mechanism of action of hydrogen peroxide is presumably by effervescent cleansing by peroxidation. The risk for damaging surrounding bone and soft-tissue structures is markedly lower for hydrogen peroxide than for cryosurgery, phenol, and argon beam coagulation. Nicholson and colleagues[19] found a statistically significant amount of cell death associated with exposing osteoblasts and GCTs of bone to hydrogen peroxide. Again, there has not been any long-term clinical follow-up, but hydrogen peroxide certainly has fewer possible adverse effects and is worth consideration.

In their 2005 review, Veth and colleagues[12] compared 5 studies that involved GCT of bone and multiple methods of surgical adjuvant treatment. Local recurrence rates were 27% after curettage only, 25% after phenol application, 7.9% after cryosurgery, and 0% after wide en bloc incision.

We contend that, with a combination of prudent reconstruction and controlled liquid nitrogen application by pressurized spray, pathologic fractures can be minimized or prevented. All 42 patients in our study were treated with pressurized-spray cryosurgery, and there were no pathologic fractures. Comparison of our 0% fracture rate with the 17% rate found for 60 patients who underwent direct-pour cryotherapy[14] (historical control) confirmed the statistical significance of our findings ($P = .003539$, 1-tailed, Fischer exact test).

More studies of the physiology of cryosurgery may shed light on why treatment with direct-pour (vs pressurized-spray) liquid nitrogen is associated with a higher rate of pathologic fracture. According to cryobiology, 5 mechanisms are responsible for the cytotoxic effect of liquid nitrogen: thermal shock, electrolyte changes, formation of intracellular ice crystals and membrane disruption, denaturation of cellular proteins, and microvascular failure.[5,20-24] Formation of ice crystals is thought to be the main cause of cell necrosis. Studying the direct-pour technique, Malawer and colleagues[5,25] found that necrosis extended 7 mm to 12 mm around the circumference of the cavity and that necrosis to such depth altered and delayed reossification. In their early studies, Marcove and colleagues[2] reported that 3 freeze–thaw cycles produced tumor cell death 2 cm from the cavity margin. We believe that cell death and bone necrosis are the driving forces for structural weakening and subsequent pathologic fracture. Dabak and colleagues[16] contended that use of pressurized spray prevents necrosis because it allows for rapid evaporation and reduction in pathologic fracture. Along these lines, we postulate that the control afforded by pressurized spray results in decreased depth of necrosis and is directly responsible for the reduction in pathologic fractures. Future animal studies that directly compare the

effects of direct-pour and pressurized-spray cryotherapy on bone may provide more insight.

One limitation of our study is that its follow-up periods were shorter than those of other studies. We believe that the 6-month follow-up cutoff is a valid minimum level because of the pathophysiology of bone necrosis and healing. Veth and colleagues[12] stated that bone strength is weakest between the immediate postoperative period and 4 months after surgery. Bickels and colleagues[9] agreed and reported that bone repair begins at 2 months and that only after 6 months is new bone formation sufficient to prevent pathologic fracture. We contend that pathologic fracture would likely occur before 6 months, as the weakening of bone structure reaches its nadir by then, and patients have been returned to activity and subjected to all the normal forces that would be responsible for pathologic fracture. However, it is important to note that pathologic fracture has been reported out until postoperative year 5.[14] More studies are needed to delineate the strength of bone as it heals.

The 2 patients who sustained traumatic fractures are of particular interest. We contend that they can be separated from the pathologic group, as other investigators have done likewise.[14] We agree that tumor removal physically weakens bone, regardless of technique, but we believe that these 2 traumatic fractures would have occurred nevertheless, with or without either direct-pour or pressurized-spray cryosurgery.

Meticulous operative prophylaxis, including internal fixation, cementation, bone grafting, and postoperative prophylaxis with bracing and limitation of activities, has reduced postoperative fractures. We believe that the pressurized-spray technique is another mechanism for reducing the fracture rate associated with use of liquid nitrogen as an adjuvant treatment in benign and low-grade malignant bone tumors.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.