6

The Biology and Role of Cryosurgery in the Treatment of Bone Tumors

Jacob Bickels, Isaac Meller and Martin Malawer

OVERVIEW

The application of liquid nitrogen as a local adjuvant to curettage in the treatment of bone tumors was first 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 has been 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. This chapter reviews the biological effect of cryosurgery on bone, surgical technique, and current indications for its use.

INTRODUCTION

Cryosurgery is the therapeutic use of cold to induce tissue necrosis with ablative intent. The first report of the use of local freezing as a treatment modality is attributed to Dr. James Arnott, who described in 1850 the direct application of a salt-ice mixture to various skin lesions.[1] 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 in the treatment of various benign and malignant lesions and achieved good results in terms of local tumor control and residual scarring.[2]

In 1962 Cooper described a cryotherapy unit in which LN was circulated through a hollow metal probe.[3] 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 –196°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.[2] Gage *et al.* treated malignant soft-tissue lesions of the oral cavity with cryotherapy and observed that the adjacent frozen bone eventually healed.[4] In their classic study Gage *et al*. used a closed system of latex tubes with LN circulating within coils surrounding the diaphyses of dog femora.[4] LN was used as a cryogenic agent because of its capability to induce rapid freezing of large lesions. The procedure was demonstrated to induce bone necrosis, followed by slow healing and new bone formation.[4–6]

The first use of cryosurgery in conjunction with orthopedic surgery is attributed to Marcove and Miller, who described an "open system" technique that entailed pouring LN directly into a tumor cavity.[7] They treated a 48-year-old male with a painful metastatic lung carcinoma to the proximal humerus that was resistant to radiation therapy. The patient experienced complete relief of his pain following treatment.[7] Liquid nitrogen was shown to achieve local tumor control with minimal bone and functional loss, and cryosurgery was soon practiced in conjunction with surgery for a large variety of bone tumors.[7–10]

Despite its demonstrated benefits, LN is a powerful local adjuvant that, when not used with caution, may cause significant injury to the adjacent rim of bone, cartilage, and soft tissues and result in secondary fracture, skin necrosis, infection, and temporary neuropraxia.[7,8,11] The early series had high complication rates that reflected an initial failure to appreciate these potentially destructive effects and establish an appropriate surgical technique. This high complication rate gave this modality a poor reputation, and during the past 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 in the treatment of liver metastases[12,13] and genitourinary malignancies.[14–16] In the field of orthopedic oncology, cryosurgery was shown to be a curative procedure in treatment of benign-aggressive and low-grade malignant bone tumors. Cryosurgery could also achieve local tumor control and symptomatic relief in metastatic bone.[17–23] This chapter reviews 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.[24] Cryosurgery utilizing LN is effective in the treatment of bone tumors because bone necrosis occurs at temperatures below –21°C.[4,25] 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.[26–31] 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. These changes are explained by increased thermal conductivity within the frozen lesion that results from an alteration in the basic structure of the tissue and are proportional to the time of exposure to LN.[4,24]

Histological evaluation of the cortex, immediately following cryosurgery, shows minimal changes. The extent of cortical injury does not become known 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.[4–6,28] Bone repair, beginning in the periphery of the bone cavity, occurs slowly and is first evident at the seventh to eighth week. Only after 5–6 months is the new bone formation sufficient to prevent pathologic fracture. The histological features after repeated freeze–thaw cycles are almost identical to those described for a single episode of freezing.[4]

Malawer *et al.* demonstrated a 7–12-mm rim of bone necrosis with no effect on articular cartilage when liquid nitrogen was utilized in a dog model (Figure 6.1).[28] Marcove *et al.* stated that three freeze–thaw cycles produce tumor cell death up to 2 cm from the cavity margin.[10] This extent of bone destruction makes cryosurgery, which is by definition an intralesional surgical modality, as effective as a wide resection in the treatment of benign-aggressive, low-grade primary bone sarcomas, or metastatic lesions.[8,9,17,22] 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 expected 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.[17,32]

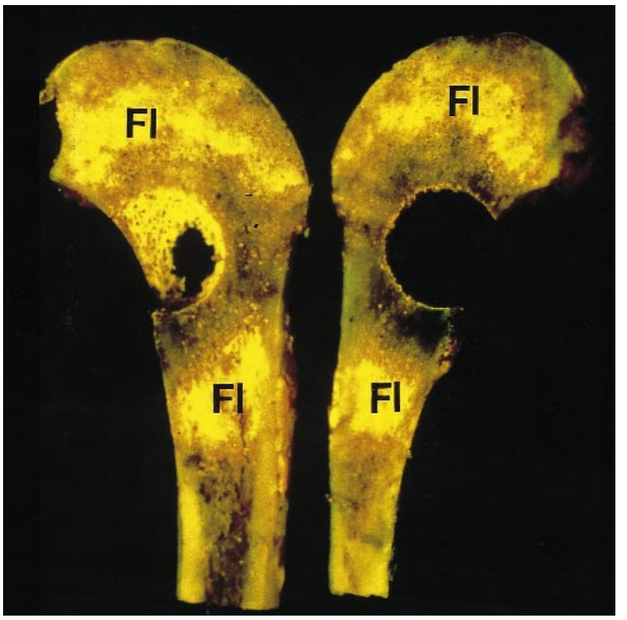


Figure 6.1 Tetracycline fluorescence of a dog femora following cryosurgery demonstrates a circumferential rim of no fluorescence around the cavity, which is the result of bone necrosis. The outer rim of fluorescence (Fl) corresponds to attempted bony repair in the adjacent viable tissue.

SURGICAL TECHNIQUE

Although a simple procedure, cryosurgery can cause significant 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 during the procedure to decrease 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. Violation of the joint cavity must be avoided because of the possibility that it may be contaminated by tumor cells and the risk of injury to the cartilage following direct exposure to LN. 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 in order to reduce the stress rising effect (Figure 6.2).

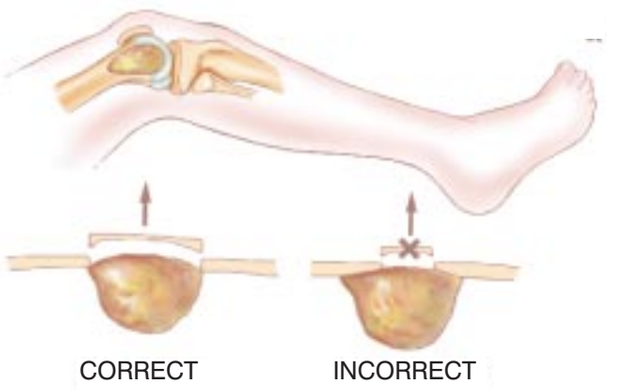


Figure 6.2 A large cortical window, the size of the largest diameter of the lesion, is essential for adequate exposure. A smaller window is not sufficient for complete curettage and burr drilling of the tumor.

Curettage

All gross tumor is removed with hand curettes. After the neoplastic tissue is 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 with Midas Rex® (Midas Rex, Forth Worth, TX) or Black Max® (Anspach, Lake Park, FL; Figures 6.3, 6.4).

Cryosurgery

Before introduction of the LN, bony perforations are identified and sealed, and the surrounding skin, soft tissues, and neurovascular bundle are protected by mobilization and shielding with Gelfoam® (Upjohn, Kalamazoo, MI). Large skin flaps are retracted to protect them from possible spillage of the LN.

Liquid nitrogen can be applied to a bony cavity by direct pour (open system) or by perfusing it through metal probes.[2,3,33] 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 are determinators of the chosen technique. Most bone lesions have a large, irregular inner wall, and use of the open system makes it possible to homogeneously spread the LN throughout the cavity. Liquid nitrogen spray is an "open system" modality, used for unique anatomic locations in which pouring of LN is not technically feasible (for example, deep-seated pelvic lesions). 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 within 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 decrease the possibility of thermal injury (Figures 6.5–6.8). In each cycle, LN is left in the cavity until it has completely evaporated. Each cycle lasts 1–2 min and is proportional to the volume of poured LN. Spontaneous thaw is then allowed to occur over a period of 3–5 min. Once the temperature of the cavity rises above 0°C the cycle is considered complete. Two freeze–thaw cycles are administered, 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 6.9–6.15). The subchondral surface is reconstructed with bone graft 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.[17] 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 performed.

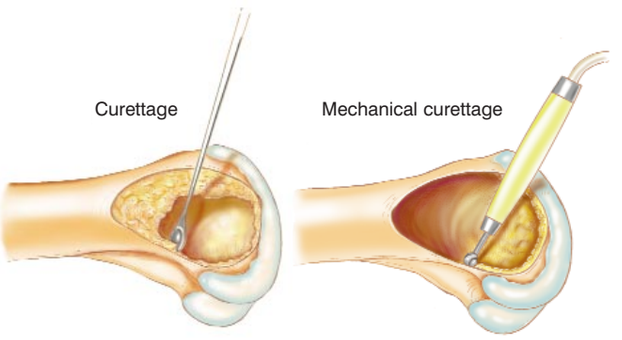


Figure 6.3 Curettage of the tumor cavity is followed by meticulous burr drilling until no tumor matrix is seen.

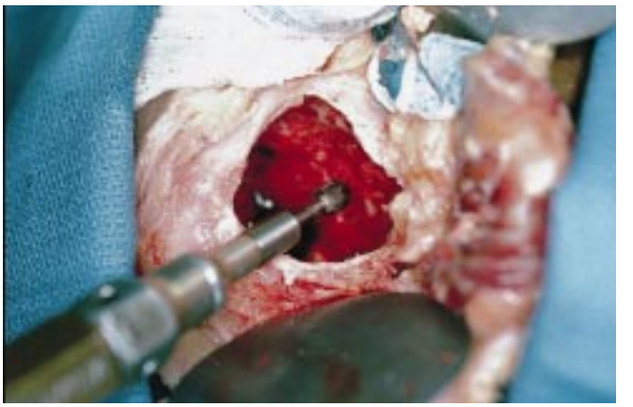


Figure 6.4 Burr drilling of a tumor cavity using the Midas Rex® system (Midas Rex, Forth Worth, TX).

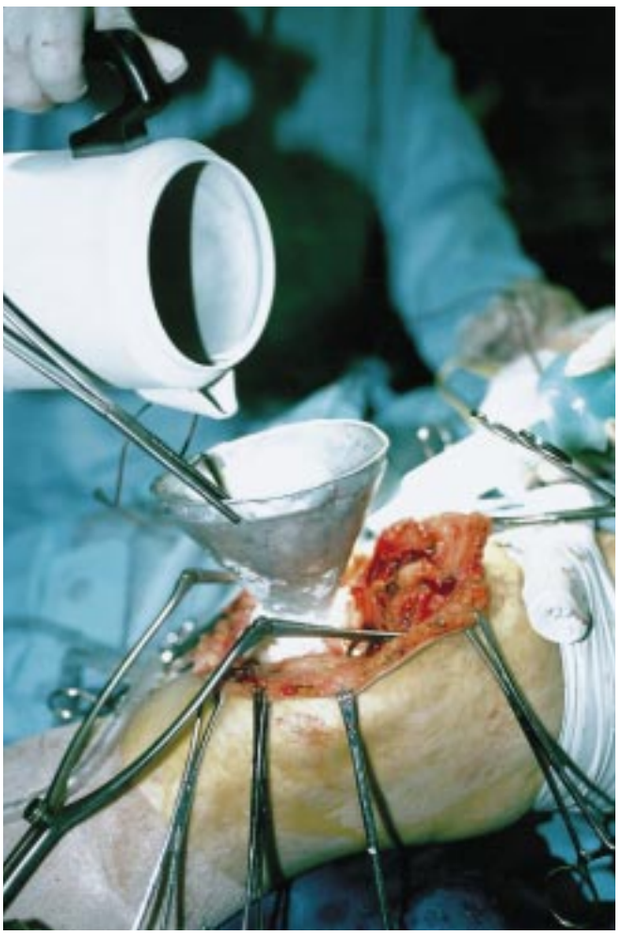


Figure 6.5 Liquid nitrogen is poured through a stainless-steel funnel. Temperature within the cavity, as well as in the surrounding bone and soft tissues, is monitored with thermocouples. Soft tissues are protected with Gelfoam® and irrigated continuously with warm saline solution.

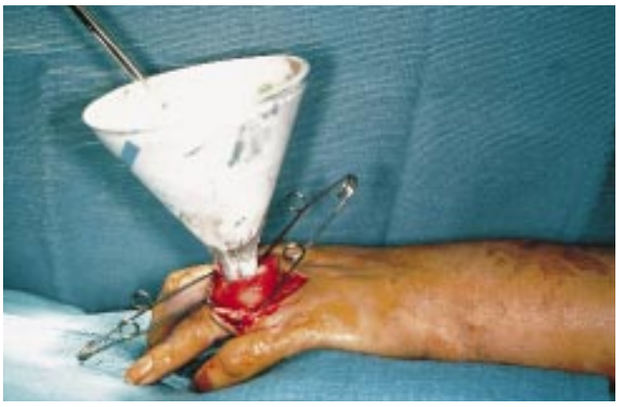


Figure 6.6 Cryosurgery of the proximal phalanx of the fourth finger.

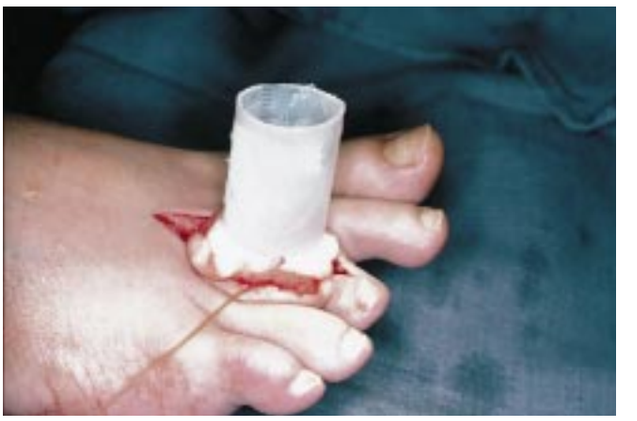


Figure 6.7 Cryosurgery of the proximal phalanx of the third toe. Mobilization and protection of the soft tissues is practiced in all anatomic locations.

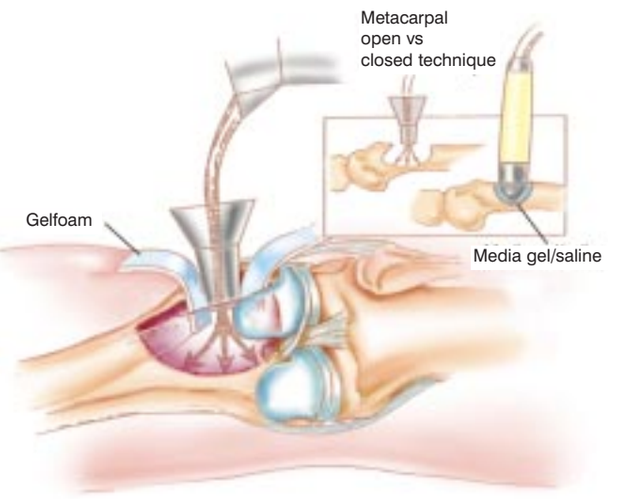


Figure 6.8 Illustration of the direct pour (open system) technique of cryosurgery.

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 is progressing satisfactorily, weight-bearing is allowed. Patients are instructed to avoid high-impact activities for 6 additional months.

Complications

The exposure of normal bone and soft tissues (skin, muscles, nerves, and blood vessels) to the freezing effect of LN can result in significant morbidity. Early studies of the use of cryosurgery in the treatment of bone

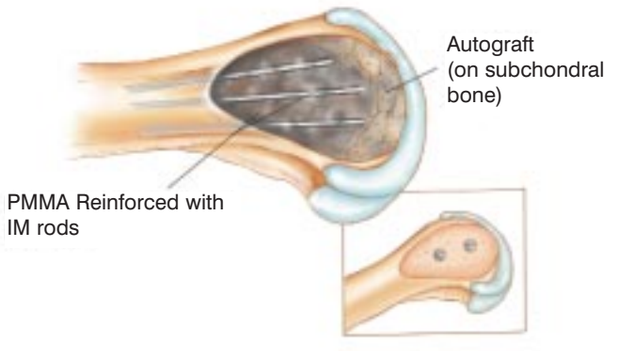


Figure 6.9 Reconstruction of the tumor cavity, using subchondral bone graft, followed by intramedullary hardware and polymethylmethacrylate. That type of composite reconstruction is used in all anatomic locations.

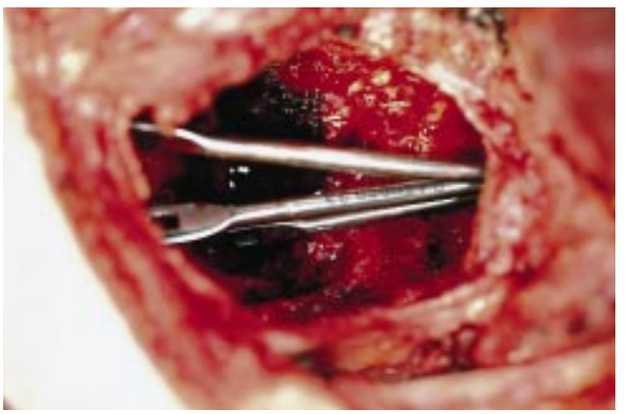


Figure 6.10 Reconstruction of the proximal tibial metaphysis with Ender rods.

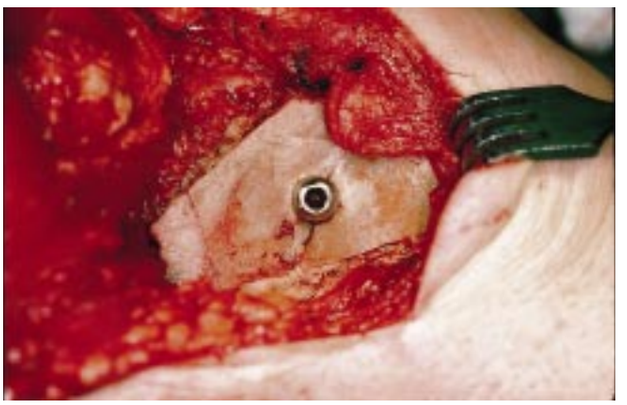


Figure 6.11 Following cementation, the cortical window is covered with autologous corticocancellous iliac bone graft.

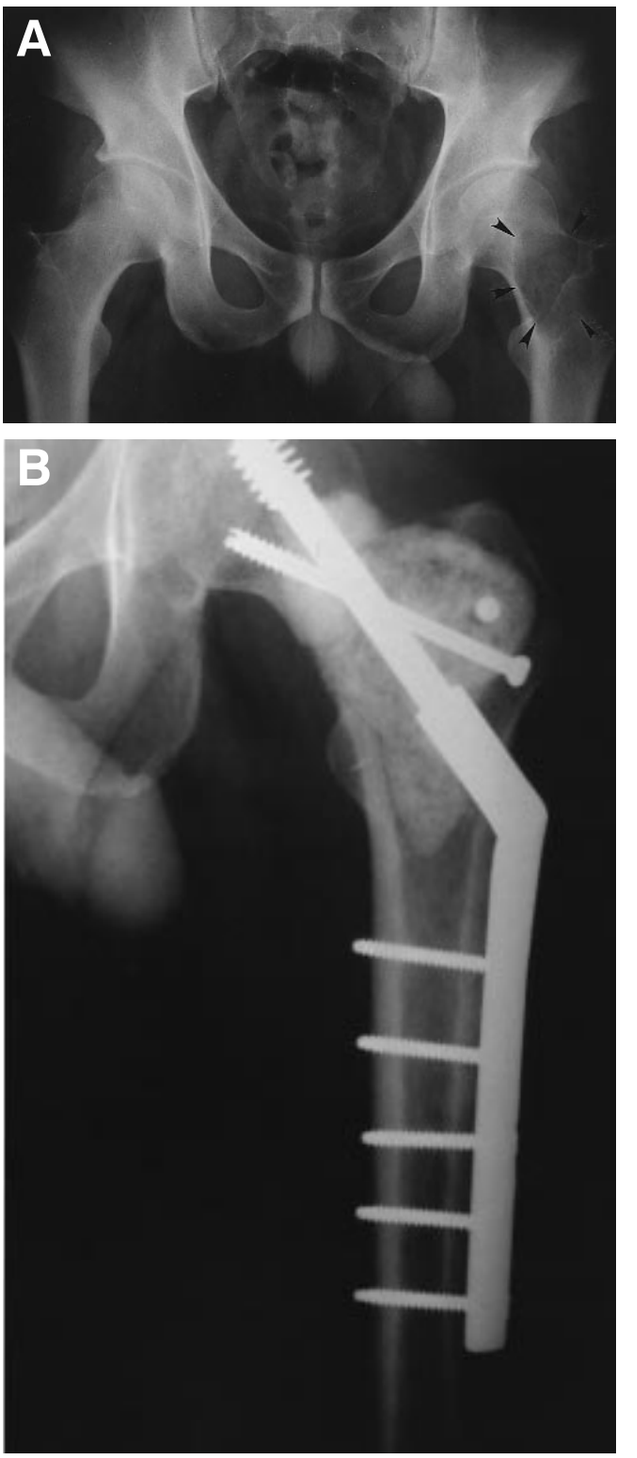
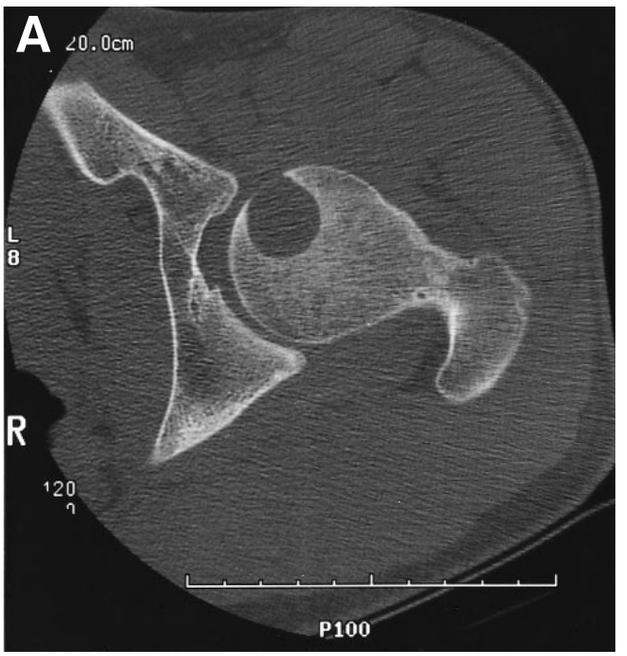


Figure 6.12 (**A**) Giant cell tumor of the proximal femur (marked with arrows) in a 31-year-old patient. (**B**) Following cryosurgery the tumor cavity was reconstructed with subchondral bone graft, PMMA, and supported with a side plate, sliding nail, and a screw. The cortical window was covered with a corticocancellous bone graft.



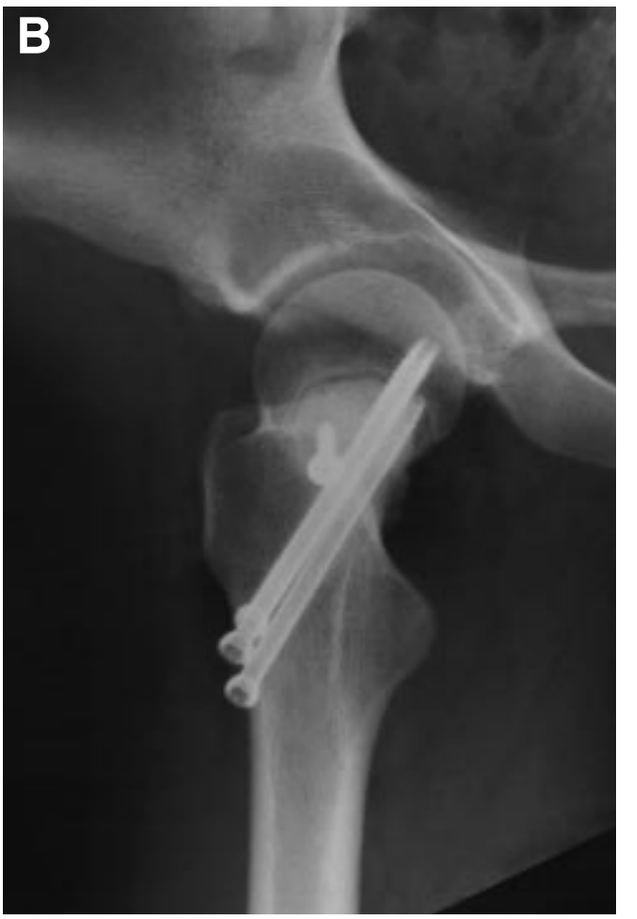


Figure 6.13 (**A**) Computed tomography of the femoral head of a 19-year-old patient, showing a chondroblastoma. Due to its anterior location the femoral head and neck were exposed using the Watson–Jones approach without dislocation of the femur. Curettage, burr drilling, and cryosurgery were performed. (**B**) These were followed by autologous iliac bone graft, reinforcement with PMMA, and internal screw fixation.

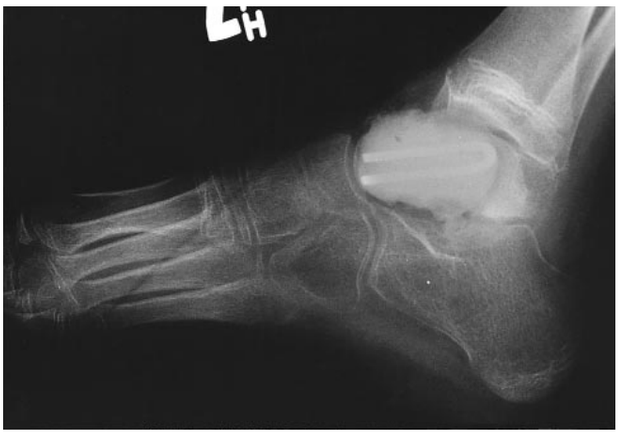


Figure 6.14 Cryosurgery of the talus for a giant-cell tumor of bone. Tumor cavity was reconstructed with subchondral bone graft, PMMA, and internal fixation.

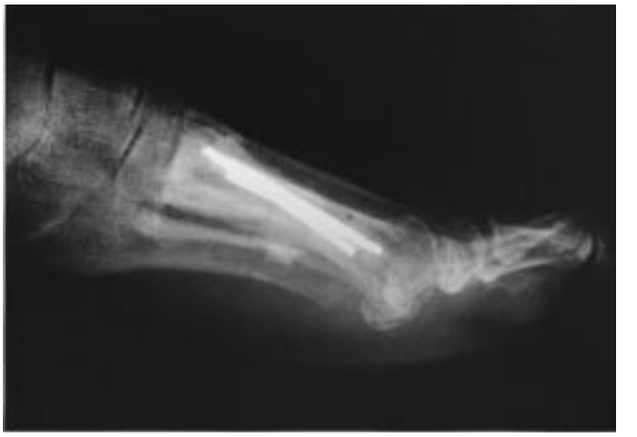


Figure 6.15 Cryosurgery of the first metatarsal for a giant-cell tumor of bone. Tumor cavity was reconstructed with subchondral bone graft, PMMA, and internal fixation.

tumors reported high complication rates, mostly pathological fractures and infection (Table 6.1). Many of these early investigators did not recognize the importance of soft-tissue protection, use of PMMA and internal fixation for reconstruction, and avoidance of significant impact on the operated extremity until healing was complete. Gage *et al.* performed cryosurgery on 34 dog femora and documented a 32.3% pathologic fracture rate when activity was not restricted and the operated bone was not protected.[4] Marcove *et al.* practiced cryosurgery prior to the use of PMMA combined with onlay bone graft and/or internal fixation.[10] They made only a minimal attempt to reconstruct the bone defect remaining after curettage and cryosurgery and reported a postoperative fracture rate of 25% in the early series (Figure 6.16). Malawer *et al.* reported a 5.9% rate of pathologic fractures following cryosurgery among 102 patients, treated with cryosurgery for giant-cell tumor of bone.[17] 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.*, who used this technique, reported no cases of infection and only three cases (2.9%) of partial skin necrosis.[17] The latter were the result of contact with leaking LN and were satisfactorily managed with nonsurgical treatment. Nerve palsy after exposure to LN occurs in less than 1% of patients and is usually transient.[17,20,33]

CLINICAL APPLICATION

Table 6.2 summarizes the reported series on bone tumors treated with cryosurgery. The most extensive orthopedic surgical experience with cryosurgery, by far, has involved giant-cell tumor (GCT) of bone, a benign-aggressive primary bone tumor. Seventy percent 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.[34] Because wide excision of these tumors would cause significant functional limitation, due to their proximity to the joint, intralesional procedures have been common practice; however, the rate of local recurrence, mainly after curettage, has been unacceptably high (i.e. 40–55%).[35–38] The introduction of LN as an adjuvant to meticulous curettage and burr drilling significantly lowered the recurrence rate; Malawer *et al.* used cryosurgery in the treatment of GCT of bone and reported a 2.3% recurrence rate among patients treated primarily with cryosurgery.[17]

Marcove and Miller used cryosurgery to treat a variety of benign and malignant bone tumors and concluded that it should be reserved for benign-aggressive bone tumors.[7] Surgical treatment of high-grade primary bone sarcoma necessitates wide excision of the tumor with its soft-tissue component; any violation of the tumor margins is associated with a high risk of local tumor recurrence.[39] Cryosurgery is not an appropriate surgical modality for high-grade primary bone sarcomas for its being an intraosseous procedure with minimal effect on the soft-tissue component of the tumor. Bone tumors that have minimal or no soft-tissue

Table 6.1 Summary of literature review on complication rates following cryosurgery

		Complications					
Author/year	*Cases*	*Fracture*	*Infection*	*Skin necrosis*	*Join 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 1997	26	1	2	–	–	1	–
Schreuder 1998	26	2	1	–	–	–	Venous gas embolism
Malawer 1999	102	6	–	3	2	1	–

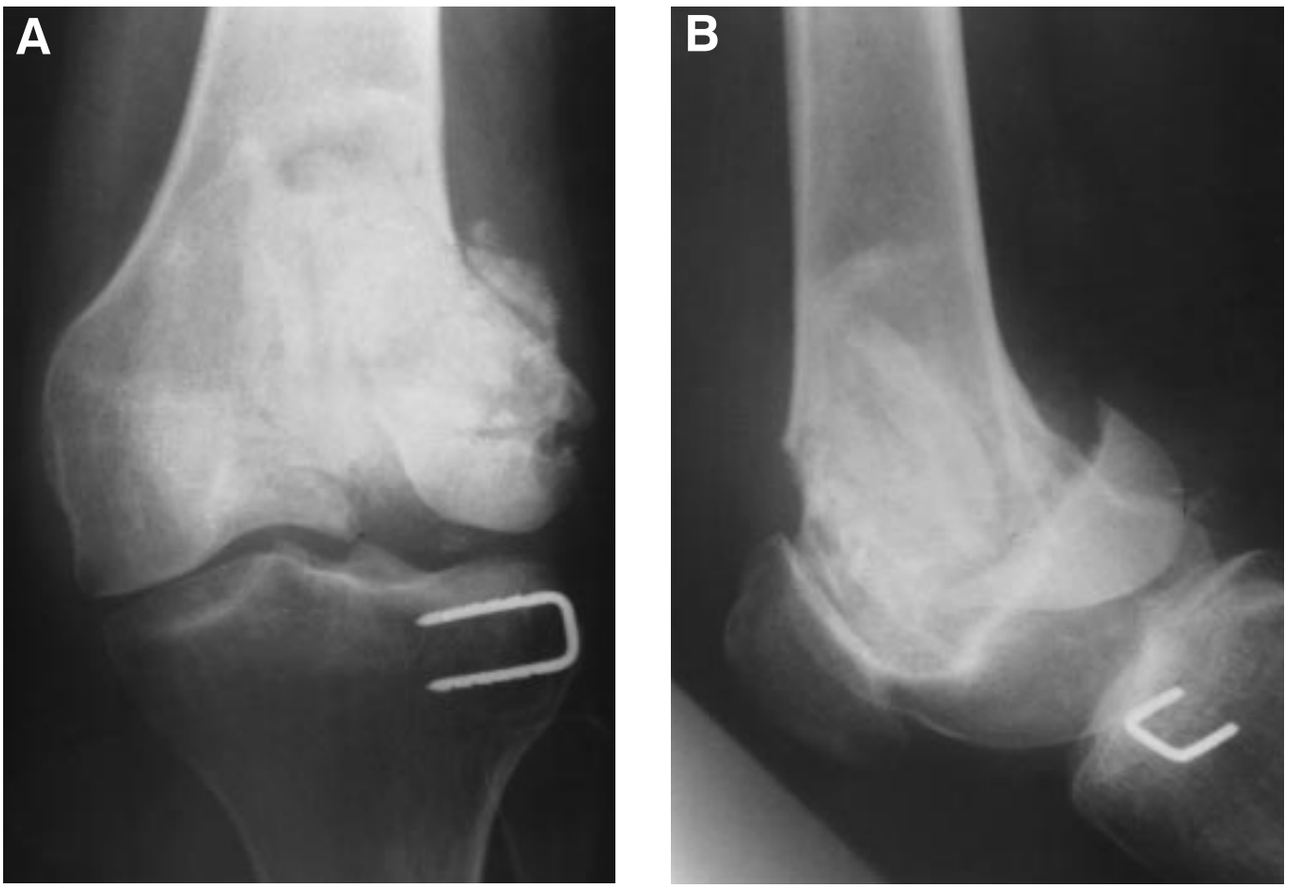


Figure 6.16 Plain radiographs of the distal femur: (**A**) anteroposterior, and (**B**) lateral views, showing a pathologic fracture of the lateral femoral condyle. The fracture occurred 18 months following cryosurgery, in which internal fixation was not used for reconstruction. Reinforcement of the tumor cavity with PMMA and internal fixation is strongly recommended in all cases.

component, such as low-grade, unicompartmental chondrosarcomas and metastatic tumors of bone, can be treated with cryosurgery.[7,9,22]

SUMMARY

Cryosurgery is an effective adjuvant to curettage for a variety of benign and malignant bone tumors. It is a curative procedure in the treatment of benign-aggressive bone lesions as well as of low-grade primary bone sarcomas, 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.

Table 6.2 Summary of literature review on bone tumors treated with cyrosurgery

Tumor type	*Author/year*
Benign aggressive lesions	
Giant-cell tumor	Aboulafia 1994; Jacobs 1985; Malawer 1991, 1999; Marcove 1969, 1973, 1978, 1994
Echondroma	Schreuder 1998
Chondroblastoma	Schreuder 1998
Unicameral bone cyst	Schreuder 1997
Aneurysmal bone cyst	Marcove 1969, 1995; Oeseburg, 1978; Schreuder 1997
Fibrous dysplasia	Marcove 1969
Hemangioma of bone	Marcove 1969
Sacral chordoma	Marcove 1969; Vries 1986
Eosinophilic granuloma	Marcove 1969
Metastatic lesions	
Carinoma of lung	Marcove 1969
Carcinoma of breast	Marcove 1969
Carcinoma of prostate	Marcove 1969
Hypernephroma	Marcove 1969, 1977
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; Marcove 1977, Schreuder 1998
Other	
Multiple myeloma	Marcove 1969

References

1. Arnott JM. Practical illustrations of the remedial efficiency of a very low or anaesthetic temperature in cancer. Lancet. 1850;2:257–316.
2. Holden HB. History and development of cryosurgery. In: Holden HB, editor. Practical Cryosurgery. Chicago: Pitman Medical Publication, 1975:1–9.
3. Cooper IS. Cryogenic surgery of the basal ganglia. J Am Med Assoc. 1962;181:600–4.
4. Gage AA, Greene GW, Neiders ME, Emmings FG. Freezing bone without excision. An experimental study of bone-cell destruction and manner of regrowth in dogs. J Am Med Assoc. 1966;196:770–4.
5. Kuylenstierna R, Lundquist PG, Nathanson A. Destruction and regeneration of jaw bone after cryogenic application. An experimental study. Ann Otol. 1980;89:582–9.
6. Schargus G, Winckler J, Schröder F, Schöfer B. Cryosurgical devitalization of bone and its regeneration. An experimental study with animals. J Maxillofac Surg. 1975;3:128–31.
7. Marcove RC, Miller TR. The treatment of primary and metastatic localized bone tumors by cryosurgery. Surg Clin N Am. 1969;49:421–30.
8. Marcove RC, Searfoss RC, Whitmore WF, Grabstald H. Cryosurgery in the treatment of bone metastases from renal cell carcinoma. Clin Orthop. 1977;127:220–7.
9. Marcove RC, Stovell PB, Huvos AG, Bullough PG. The use of cryosurgery in the treatment of low and medium grade chondrosarcoma. Clin Orthop. 1977;122:147–56.
10. Marcove RC, Weis LD, Vaghaiwalla MR. Cryosurgery in the treatment of giant cell tumor of bone. A report of 52 consecutive cases. Cancer. 1978;41:957–69.
11. Marcove RC, Lyden JP, Huvos AG, Bullough PG. Giant cell tumors treated by cryosurgery. J Bone Joint Surg. 1973; 55:1633–44.
12. Korpan NN. Hepatic cryosurgery for liver metastases. Ann Surg. 1997;225:193–201.
13. Weaver ML, Atkinson D, Zemel R. Hepatic cryosurgery in treating colorectal metastases. Cancer. 1995;76:210–14.
14. Creasman WT, Hinshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. Obstet Gynecol. 1984;63:145–9.
15. Miller RJ Jr, Cohen JK, Shuman B, Merlotti LA. Percutaneous, transperineal cryosurgery of the prostate

as salvage therapy for post radiation recurrence of adenocarcinoma. Cancer. 1996;77:1510–14.
16. Wong WS, Chinn DO, Chinn M, Chinn J, Tom WL, Tom WL. Cryosurgery as a treatment for prostate carcinoma: results and complications. Cancer. 1997;79:963–74.
17. Malawer MM, Bickels J, Meller I, Buch R, Kollender Y. Cryosurgery in the treatment of giant cell tumor. A long term follow-up study. Clin Orthop. 1999;359:176–88.
18. Malawer MM, Dunham W. Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors. Analysis of 25 patients below the age of 21. Clin Orthop. 1991;262:42–57.
19. Marcove RC, Sheth DS, Brien EW, Huvos AG, Healey JH. Conservative surgery for giant cell tumors of the sacrum. The role of cryosurgery as a supplement to curettage and partial excision. Cancer. 1994;74:1253–60.
20. Marcove RC, Sheth DS, Takemoto S, Healey JS. The treatment of aneurysmal bone cyst. Clin Orthop. 1995;311: 157–63.
21. Schreuder HW, Conrad EU 3rd, Bruckner JD, Howlett AT, Sorensen LS. Treatment of simple bone cysts in children with curettage and cryosurgery. J Pediatr Orthop. 1997; 17:814–20.
22. Schreuder HW, Pruszczynski M, Veth RP, Lemmens JA. Treatment of benign and low-grade malignant intramedullary chondroid tumours with curettage and cryosurgery. Eur J Surg Oncol. 1998;24:120–6.
23. Schreuder HW, Veth RPH, Pruszczynski M, Lemmens JAM, Koops HS, Molenaar WM. Aneurysmal bone cysts treated by curettage, cryotherapy and bone grafting. J Bone Joint Surg. 1997;79:20–5.
24. Gill W, Fraser J, Carter DC. Repeated freeze–thaw cycles in cryosurgery. Nature. 1968;219:410–13.
25. Schreuder HW, van Egmond J, van Beem HB, Veth RP. Monitoring during cryosurgery of bone tumors. J Surg Oncol. 1997;65:40–5.
26. Harris L, Griffiths J. Relative effects of cooling and warming rates on mammalian cells during the freeze–thaw cycle. Cryobiology. 1977;14:662–9.
27. Karow AR, Webb WR. Tissue freezing, a theory for injury and survival. Cryobiology. 1965;2:99–108.
28. Malawer MM, Marks MR, McChesney D, Piasio M, Gunther SF, Shmookler BM. The effect of cryosurgery and polymethylmethacrylate in dogs with experimental bone defects comparable to tumor defect. Clin Orthop. 1988; 226:299–310.
29. Mazur P. Cryobiology: the freezing of biological systems. Science. 1970;168:939–49.
30. McGann LE, Kruuv J, Frim J, Frey HE. Factors affecting the repair of sublethal freeze–thaw damage in mammalian cells. Suboptimal temperature and hypoxia. Cryobiology. 1975;12:530–9.
31. Miller RH, Mazur P. Survival of frozen-thawed human red cells as a function of cooling and warming velocities. Cryobiology. 1976;13:404–14.
32. Aboulafia AJ, Rosenbaum DH, Sicard-Rosenbaum L, Jelinek JS, Malawer MM. Treatment of large subchondral tumors of the knee with cryosurgery and composite reconstruction. Clin Orthop. 1999;307:189–99.
33. Jacobs PA, Clemency RE. The closed cryosurgical treatment of giant cell tumor. Clin Orthop. 1985;192:149–58.
34. Huvos GA. Giant-cell tumor of bone. In: Huvos GA, editor. Bone Tumors: Diagnosis, Treatment and Prognosis, 2nd edn. Baltimore: W.B. Saunders Company; 1991: 429–67.
35. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant cell tumor of bone. J Bone Joint Surg. 1987;69:106–14.
36. Goldenberg R, Campbell C, Bonfiglio M. Giant cell tumor: an analysis of 218 cases. J Bone Joint Surg. 1970;52:619–64.
37. Johnson EW, Dahlin DC. Treatment of giant cell tumor of bone. J Bone Joint Surg. 1959;41:895–904.
38. McDonald DJ, Sim FH, McLeod RA, Dahlin DL. Giant cell tumor of bone. J Bone Joint Surg. 1986;68:235–42.
39. Petersson H, Springfield DS, Enneking WF. Surgical principles. In: Petersson H, Springfield DS, Enneking WF, editors. Radiologic Management of Muskuloskeletal Tumors. Berlin: Springer-Verlag; 1987:9–13.