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ORIGINAL ARTICLE

The effect of adjuvant cryotherapy added to well-performed high-speed burr curettage on the long-term surgical outcomes of chondroblastoma cases

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ABSTRACT

Objectives: This study aims to investigate the effect of adjuvant cryotherapy added to well-performed high-speed burr curettage on the long-term surgical outcomes of chondroblastoma cases.

Patients and methods: Between January 2004 and December 2020, a total of 30 chondroblastoma cases (19 males, 11 females; median age: 18.6 years; range, 9 to 53 years) who were surgically treated were retrospectively analyzed. The pressurized-spray technique was performed using liquid nitrogen. Data including age, sex, radiological appearance, treatment modality, duration of follow-up, skin problems, and recurrence were recorded. All patients received adjuvant liquid nitrogen cryotherapy after extended intralesional curettage with high-speed burr. The bone cavity was filled with an autologous iliac crest bone graft, allograft, or polymethylmethacrylate (PMMA).

Results: The median follow-up was 54 (range, 19 to 120) months. The lesion was located around the knee in 16 (53.3%), in the shoulder in seven (23.3%), around the hip in five (16.6%), and in the ankle in two (6.6%) cases. The defect was filled with an autologous iliac crest bone graft in 28 (93.3%), an additional allograft in eight (26.7%), and PMMA in two (6.7%) cases. Local recurrence was observed in only two (6.7%) patients during follow-up. Two (6.7%) patients developed physeal growth arrest. Osteoarthritic changes were observed in two (6.7%) patients (one knee and one hip) due to the periarticular location of the tumor. Three (10%) patients had skin complications. None of the cases had a pathological fracture.

Conclusion: A well-performed extended intralesional curettage with high-speed burr is the first and essential step in treating chondroblastoma. Adding adjuvant liquid nitrogen cryotherapy with high-speed burr can improve treatment outcomes and significantly reduce the recurrence rate of this disease.

Keywords: Adjuvant, chondroblastoma, cryosurgery, curettage, recurrence.

Chondroblastoma is a sporadic benign bone tumor originating from cartilage cells. Chondroblastoma was first accepted as an entity by Kolodny[1] in 1927 and was defined as a "giant cell variant". The term chondroblastoma was introduced by Jaffe and Lichtenstein[2] in 1942 and was included in the group of chondroid tumors by distinguishing it from giant cell tumors. It accounts for less than 1% of all bone tumors and 9% of benign bone tumors.[3] Chondroblastoma is mostly located in the epiphyses of long bones, with the most common localizations being the proximal humerus, distal femur, proximal femur, and proximal tibia.[4] It is very rare to be seen over the age of 25 years, and lesions are seen mostly in adolescent patients during active epiphyseal growth. It is two times more common in males.[4,5] Patients usually present with gradually increasing pain, which is in

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the joint adjacent to the lesion and does not change in intensity with activity. In addition, effusion in the joint, limitation of movement, muscle atrophy, and disruption are other findings that can be seen.

On plain radiography, chondroblastoma is seen as a lytic area located eccentrically in the epiphysis and surrounded by a peripherally reactive, thin sclerotic rim.[6] The lesion crosses the epiphyseal line in more than half of the cases. The round or oval-shaped lesion can reach half the width of the epiphysis, which may sometimes cause an expansion in the cortex. Computed tomography (CT) and magnetic resonance imaging (MRI) can be performed to better evaluate its boundaries and content. The relationship of the lesion with the cortex is seen in more detail with a CT scan, and punctate calcifications that cannot be fully detected on direct radiography can be also visualized. In addition, MRI is helpful to reveal peritumoral edema and evaluate the relationship of the lesion with the epiphysis and joint.

Although surgical excision is the treatment of choice in chondroblastoma cases, the recommended surgical treatment for chondroblastoma varies depending on each case. Curettage has been described as either a stand-alone procedure or combined with autogenous and allogeneic bone grafting.[7,8] Successful treatment results can be obtained with extended surgical curettage, high-speed burr, and cauterization without using chemical adjuvants in locally aggressive bone tumors.[9] Filling the cavity formed after curettage with polymethylmethacrylate (PMMA) is another recommended treatment method.[8,10] Aggressive curettage and bone grafting are mostly preferred.[11] Grafting can be applied for the defect that occurs after curettage. Local recurrence rates vary between 10 and 35%.[12] It is recommended that phenol or liquid nitrogen be used as an adjuvant to reduce the possibility of recurrence.[13-16] In case of recurrence, curettage and grafting are required again. In rare cases, chondroblastoma may cause lung metastasis, which would then require a metastasectomy.[17] Risk factors for recurrence and metastasis have not been clearly defined yet. Chemotherapy and radiotherapy have no place in the treatment.

Recurrence is a significant problem in the treatment of chondroblastoma. Therefore, adjuvant treatment methods are being developed in addition to curettage to reduce recurrence. The effect of adjuvant cryotherapy added to well-performed high-speed burr curettage on the long-term surgical outcomes of chondroblastoma cases is still unclear. In the present study, the primary objective was to evaluate the long-term surgical outcomes of chondroblastoma patients treated with extended curettage using high-speed burr combined with adjuvant cryosurgery. The secondary objective was to investigate whether this additional information on patients with chondroblastoma treated with cryosurgery could significantly increase knowledge and understanding of this topic, particularly with the prospects of a large meta-analysis.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ondokuz Mayıs University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2004 and December 2020. Among a total of 3,748 patients with a bone tumor, 34 (0.9%) with chondroblastoma were screened. After the exclusion of four patients with incomplete data, a total of 30 cases of chondroblastoma (19 males, 11 females; median age: 18.6 years; range, 9 to 53 years) who were examined and surgically treated by a Multidisciplinary Bone and Soft Tissue Tumors Care Team were included.

The diagnosis was based on radiological findings, and confirmed by a histopathological examination of the curettage material after surgery. Lesions were classified according to the classification system described by Enneking[18] for staging benign neoplasms of the musculoskeletal system: Stage I, inactive or latent; Stage II, active; and Stage III, aggressive. The curetted tissues were histopathologically analyzed to confirm the diagnosis and to detect the presence of any associated aneurysmal bone cyst component. Patients were followed every three months postoperatively, both clinically and radiologically, and bone scans were performed every six months to identify any local recurrence. The patients were called for an annual check-up at the end of the first two years.

Surgical technique

Our institution uses cryosurgery as adjuvant therapy in chondroblastoma (Figure 1). The lesions were treated first by a meticulous, extensive intralesional curettage to remove all the visualized tumoral tissues through an oval window in the cortex (Figure 1a). Then high-speed burr drilling was used to destroy the remaining tumor cells on the walls of the cavity (Figure 1b). The application of liquid nitrogen with a pressurized spraying technique ensured penetration into all unhealthy tissues.

While pouring the liquid nitrogen, extra care was taken to protect the surrounding soft tissues,

including the skin and neurovascular structures. Before applying the liquid nitrogen, large, warm, wet towels were placed over the tissues surrounding the cavity for their protection. The towels were repeatedly rinsed in warm sodium saline during the procedure. The extended drain of the aspirator was used to apply liquid nitrogen directly into the cavity. One end of the drain was placed in the liquid nitrogen tank, and the other was inside the cavity (Figure 1c). The time was approximately 2 min for each freezing cycle in which liquid nitrogen was applied. Subsequently, gradual dissolution was carried out for about three to 5 min. Following each cryotherapy session, the cavity was re-irrigated with sodium saline. Three cycles of pressurized spray system cryosurgery were applied using liquid nitrogen. In each cycle, the liquid nitrogen was left in the cavity, until it was completely evaporated. Depending on the lesion size, the defects were filled with an autogenous cancellous bone graft, allograft, or polymethylmethacrylate (Figure 1d). Liquid nitrogen was applied to the lesion in every direction, until the whole cavity was frozen. Liquid nitrogen was, likewise, used for the bony window (Figure 1e). At the end of the procedure, the bone was fixed in place of the window (Figure 1f). Histopathological examinations were performed on the curetted tissue to confirm the diagnosis of chondroblastoma.

All patients were encouraged for early postoperative physical rehabilitation; however, a standard protocol could not be achieved. In addition, if the tumor was localized around any site of the weight-bearing area, weight-bearing of these patients was not allowed immediately after surgery to preserve the biological reconstruction and prevent pathological fractures that may occur due to cryotherapy. Quadriceps strengthening exercises were applied to patients with tumors localized around the knee, and passive joint movements were allowed to prevent joint contracture.

Statistical analysis

Statistical analysis was performed using the Jamovi project version 2.0.0.0 (https://www.jamovi.org), JASP version 0.14.1.0 (https://jasp-stats.org), and MedCalc version 15.2 software (MedCalc Software bvba, Ostend, Belgium). Descriptive data were expressed in median (min-max) or number and frequency,

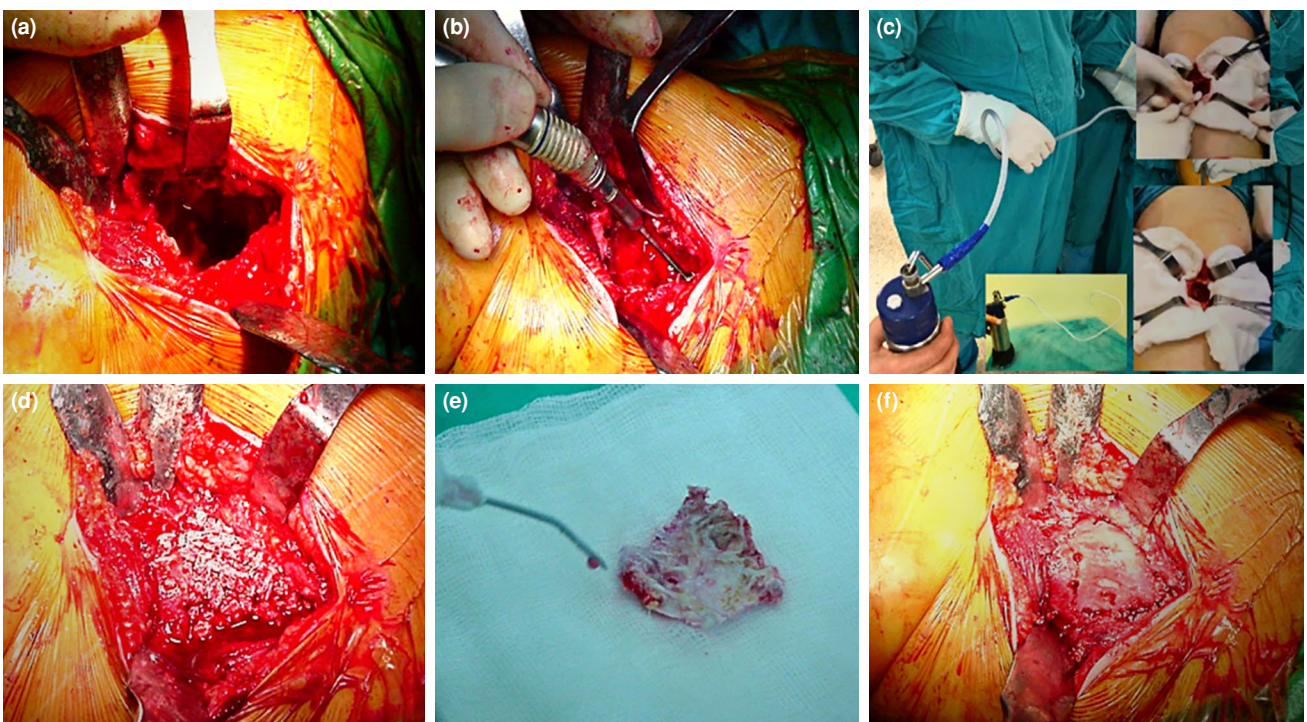


FIGURE 1. Pressurized spray technique followed by bone grafting and fixation. **(a)** The lesions were treated first by meticulous, extensive intralesional curettage to remove all the visualized tumoral tissues through an oval window in the cortex, **(b)** High-speed burr drilling, **(c)** The application of liquid nitrogen with a pressurized spraying technique, **(d)** The defects were filled with autogenous cancellous bone graft, **(e)** Liquid nitrogen was likewise used for the bony window, **(f)** Fixation of the bone window at the end of the procedure.

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where applicable. Kaplan-Meier analysis were used to estimate local recurrence-free survival. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 30 patients, 23 (76.7%) were aged between 10 and 20 years. Of these cases, 16 (53.3%) were located around the knee, seven (23.3%) were in the shoulder, five (16.6%) were around the hip, and two (6.6%) were in the ankle. According to Enneking's classification, 24 lesions were active (80%), and six were aggressive (20%). Local recurrence was observed in two (6.7%) patients during the 10-year follow-up. Two (6.7%) patients developed physeal growth arrest. Osteoarthritic changes were observed in two (6.7%) patients (one knee and one hip) due to the periarticular location of the tumor. Three (10%) patients had skin complications. None of the cases had a pathological fracture. The main presenting symptoms were pain in 25 (83.3%) patients and swelling in 12 (40%) patients. The median duration of symptoms at the time of presentation was 14.8 (range, 5 to 34) months. Aneurysmal bone cyst components were noted histologically in three of the 30 tumors (10%). These tumors were classified radiologically as aggressive lesions (Table I).

All patients were treated with extended curettage using high-speed burr combined with adjuvant cryosurgery. The defect was filled with an autologous iliac crest bone graft in 28 (93.3%), and additional allograft in eight (26.7%), and PMMA in two cases (6.7%). All bone grafts were incorporated and remodeled, resulting in total weight-bearing capacity in all patients. The median time for bone healing was 8.6 (range, 5 to 11) months (Figure 2). The diagnosis of chondroblastoma was confirmed

TABLE I
Demographic, clinical, and tumor characteristics of chondroblastoma patients

Variables	n	%	Median	Range
Age (year)			18.6	9-53
The mean follow-up period (month)			54	19-120
The average duration of symptoms (month)			14.8	5-34
Sex				
Male	19	63.3		
Female	11	36.7		
The main presenting symptoms				
Pain	25	83.3		
Swelling	12	40		
Tumor localization				
Around the knee joint	16	53.3		
Around the shoulder joint	7	23.3		
Around the hip joint	5	16.6		
Around the ankle joint	2	6.6		
Tumor stage (Enneking)				
Stage 1	0	0		
Stage 2	24	80		
Stage 3	6	20		
ABC Component	3	10		
Grafting				
Autograft	28	93.3		
Allograft	8	26.7		
Cement (PMMA)	2	6.7		
Recurrence	2	6.7		
Complications				
Physeal growth arrest	2	6.7		
Osteoarthritic changes	2	6.7		
Skin complications	3	10		
Pathological fracture	0	0		

ABC: Aneurysmal bone cyst; PMMA: Polymethylmethacrylate.

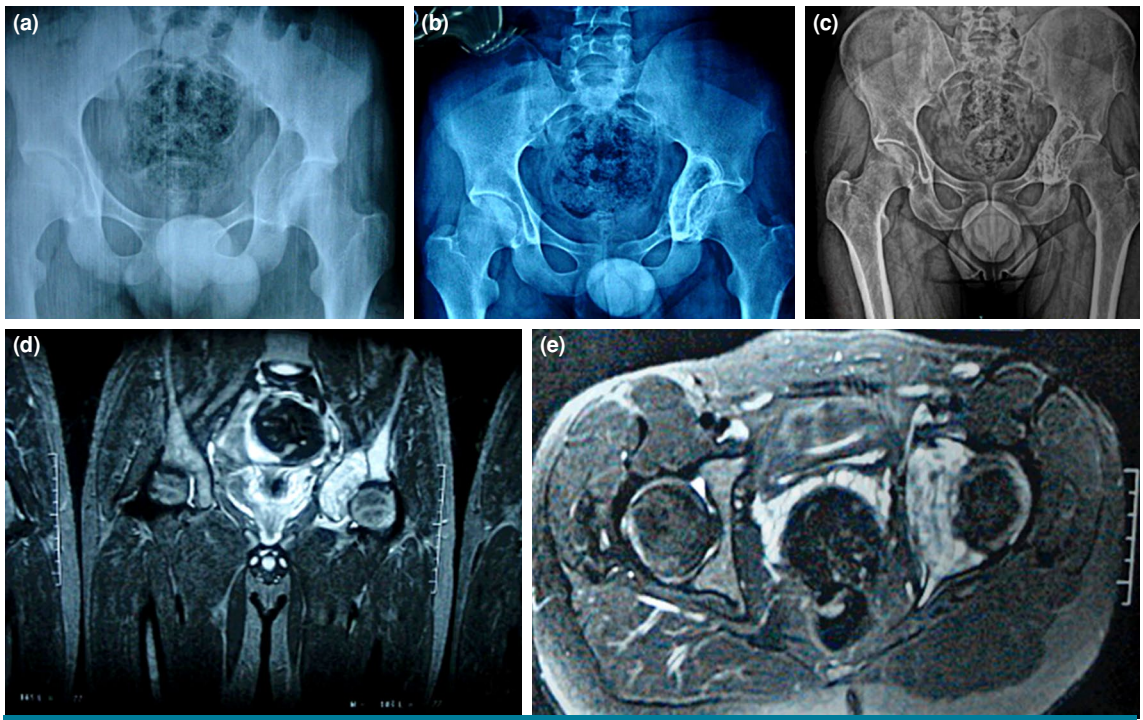


FIGURE 2. An 18-year-old male patient with a chondroblastoma around the left acetabulum, preoperative X-ray **(a)**, coronal and axial sections of MRI **(d-e)**. Following extensive curettage and cryotherapy, the defect was filled with autologous bone grafting with the same procedure. The early postoperative X-ray **(b)** and the X-ray at nine years (108 months) of follow-up **(c)**. During the follow-up period, no complications developed, such as local recurrence, only a slight degeneration on the roof of the acetabulum.
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by histopathological examination. There was no neurovascular complication in any patient after surgery or during the follow-up period. The median follow-up was 54 (range, 19 to 120) months.

Local recurrence of the tumor occurred in only two of 30 (6.7%) cases. One lesion was in the distal femur, and the other was in the proximal femur. These lesions were initially classified as Stage III (aggressive) according to Enneking's classification as assessed by radiography. Relapse occurred six months later in one case and eight months later in the other. In both cases, the bony cavity formed was filled using only allograft. The diagnosis was based on the radiological appearance of the lesion and the return of clinical symptoms after surgery. The MRI images showed tumor recurrence, and histological examination confirmed chondroblastoma recurrence. The patients were treated with the same technique and recovered without recurrence by the final follow-up (range, 64 to 55 months).

None of the patients developed pathological fractures after cryotherapy. A 10-year-old patient (3.3%) developed physeal growth arrest in the medial femoral condyle of the right knee and progressively developed varus deformity in the knee. The deformity was unacceptable, necessitating correction with distal femoral osteotomy.

DISCUSSION

In the present study, we investigated the role of intraregional, well-performed, high-speed burr curettage and the application of adjuvant cryotherapy in chondroblastoma cases. The main result is that local recurrence was observed in only two patients (6.7%) at a median follow-up of 54 months.[19] In addition, consistent with the literature, the median age of the patients in this study was 18.6 years, of which 76.7% were between the ages of 10 and 20 years. The most common localizations of chondroblastoma are the proximal part of the tibia, the proximal part of the femur, the distal part of the femur, and the proximal part of the humerus.[3,4] In this study, chondroblastoma was observed around the knee in most of the patients. Chondroblastoma is rarely incidentally found on plain radiographs

and is typically symptomatic. The most typical manifestation is local pain, which may persist for a long time. Localized edema, swelling, effusion, and limitation of joint movement are some other symptoms. The vast majority of our patients were male, consistent with previous series.[4,20]

The differential diagnosis may not be difficult, since there are few epiphyseal lesions. However, the differential diagnosis of chondroblastoma, clear cell chondrosarcoma, giant cell tumor, and aneurysmal bone cyst can be challenging due to the radiological difficulty. Chondroblastoma may have giant cells that can be confused with giant cell tumors in histology. Some cases with chondroblastoma are combined with a secondary aneurysmal bone cyst on plain radiographs, and the exact diagnosis needs histological confirmation.[21] A giant cell bone tumor may be also located in the epiphysis, but this tumor usually occurs after epiphyseal closure, unlike chondroblastoma. In addition, intraosseous abscesses, synovitis, osteonecrosis, and intraosseous ganglia should be considered in the differential diagnosis with chondroblastoma. One of the most important bends on the difficult road to the right treatment is to make the correct diagnosis. Therefore, differential diagnosis of chondroblastoma should be kept in mind.

Currently, there is no standard treatment for chondroblastoma. The recommended treatment is extended intralesional curettage, and the defect must be filled with grafting. Curettage has been described as performed alone[22,23] or with adjuvants such as high-speed burring,[21] cryosurgery,[13] hydrogen peroxide,[24] and cauterization.[9] Defects are filled with bone grafting or polymethacrylate. *En-bloc* resection[21] and percutaneous radiofrequency heat ablation (RF)[25] are the other treatment options for chondroblastoma. However, RF is recommended for smaller lesions, and more significant lesions at risk of damaging articular cartilage/growth plate, incomplete tumor ablation, and mechanical failure following RF treatment.[26]

Local recurrence of chondroblastoma is a significant challenge for the physician. The local recurrence rate varies according to treatment methods. Local recurrence rates after curettage and grafting have been reported to be between 10 and 35%.[12,27,28] Due to the concerns of surgeons that aggressive curettage can damage the growth plate in the pediatric population, it is thought that recurrence is probably caused by insufficient curettage.[8,29] This refers to that local adjuvants are more critical for the total eradication of the tumor. In the current study, osteoarthritis was observed in two patients during follow-up. However, when previous images were reviewed, this might have been due to the aggressive behavior of the tumor rather than damage to the growth plate during the surgical procedure. Consistent with this opinion, Springfield et al.[30] reported that, in a patient in whom the related joint or growth plate was damaged, this was due to the aggressive behavior of the tumor, but not to surgical treatment itself.

As a result, the need for adjuvant treatment arises. High-speed burring (local recurrence rates, 3.2% and 0%, respectively),[31,32] phenol (local recurrence rates, 10% and 9.7%, respectively),[16,33] liquid nitrogen (local recurrence rates, 7.1%, 0%, 7.5%, 7.1%, and 5.5%, respectively),[13-15,34] electrocauterization (local recurrence rates, 9.9% and 21.4%, respectively),[9,35] and cementing (local recurrence rate, 4.2%,)[36] have been used as local adjuvants and have been shown to decrease recurrence rates. Local adjuvants can significantly influence the control of local recurrence. In an analysis of 62 chondroblastoma patients, Hsu et al.[32] suggested curettage and high-speed burring as an efficient approach for treating chondroblastoma of the bone, whether in the non-aggressive or aggressive stage. Algawahmed et al.[37] also examined 387 patients with benign bone tumors and compared the local recurrence rates of 64 patients treated with curettage and high-speed burring alone versus 323 patients treated with high-speed burring and a local adjuvant. According to the findings, high-speed burring alone and burring combined with additional adjuvants did not significantly differ. After substantial curettage, high-speed burring may continue to be used more frequently than other local adjuvants. Due to the heat released during solidification, cement may cause physical destruction and, therefore, cement is a contentious therapy option for chondroblastoma in the epiphysis. The same risk is present in cryosurgery.[13] In the current study, a 10-year-old patient (3.3%) developed physeal growth arrest in the medial femoral condyle of the right knee and progressively developed varus deformity in the knee. The deformity was unacceptable, necessitating correction with distal femoral osteotomy.

Cryosurgery is an adjuvant therapy capable of preventing local recurrence and has good functional results.[34] It can be used in the treatment of aggressive benign tumors, low-grade malignant sarcomas, and metastatic bone tumors. The formation of intracellular

ice crystals and membrane disruption are the main mechanisms. Other mechanisms include cytotoxicity, electrolyte changes, denaturation of cellular proteins, and microvascular insufficiency.[38-40]

Liquid nitrogen can be poured directly into the bone cavity (open system), perfused through metal probes (closed system),[41] or applied by a pressurized spray system. The cryosurgery method used in this series is a modified open technique, which combines direct pouring and a pressurized spray system. Compared to the direct pouring technique, soft tissue injury and bone necrosis are less common due to the spray technique's rapid evaporation during cryosurgery application. In an animal study by Keijser et al.,[42] in which liquid nitrogen was applied at -50°C, there was found to be osteonecrosis within 2 mm of the border of the treated bone. This is considered an oncologically safe distance. Mashhour and Rahman[13] found the local recurrence rate to be 7.1% after adding adjuvant intralesional cryotherapy to the curettage procedure. Although cryosurgery has satisfactory results, it may cause complications such as pathological fracture, skin necrosis, significant injury to the adjacent rim of bone, infection, and temporary neuropraxia.[43]

In the current study, all patients underwent extended curettage, high-speed burr drilling, cryotherapy, and bone grafting of the cavity, except two patients whose defect was filled with PMMA. The main result is that local recurrence was observed in only two (6.7%) patients at a median follow-up of 54 months. This can be attributed to the use of aggressive curettage, a high-speed burr procedure, and then cryotherapy as an adjuvant. This can be considered a successful treatment option in the management of chondroblastoma cases and in reducing the recurrence rate, which is one of the leading causes of treatment failure.

Nonetheless, there are some limitations to this study. First, this is a single-center, retrospective study, including only a small number of patients, possibly due to the rare prevalence of the tumor. Second, non-surgical treatments for chondroblastoma were not mentioned. The benefits and disadvantages of non-surgical treatment are still unknown. Although there are some new technologies in cryoablation, further studies are needed to investigate the efficacy and side-effects of this adjuvant therapy, particularly the cytotoxicity of cryotherapy. Materials filling the bone defect may also affect outcomes such as local recurrence and bone healing, but this is not the subject of this study. Finally, many studies have reported that local adjuvants can decrease the local recurrence of some benign and aggressive tumors. For chondroblastoma, intralesional curettage combined with local adjuvant cryotherapy can obtain a satisfactory outcome.

In conclusion, a well-performed extended curettage is the first and most crucial step in the treatment of chondroblastoma with low local recurrence rates. Adding adjuvant liquid nitrogen cryotherapy with high-speed burr can improve treatment outcomes and significantly reduce the recurrence rate of this disease. In the standard treatment of chondroblastoma, the use of adjuvant liquid nitrogen cryotherapy after a well-executed extended curettage can be recommended to reduce local recurrence rates. However, further large-scale studies may be helpful to confirm the effectiveness of cryosurgery on the local recurrence rate.

Ethics Committee Approval: The study protocol was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (date: 17.07.2020, no: 2020/440). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient and parents and/or legal guardians of pediatric patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Material preparation, data collection, and analysis were performed by A.Y., H.S.C., N.D.; Wrote the first draft of the manuscript: A.Y.; H.S.C., H.Ç., and all authors commented on previous versions. All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

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