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BRISTOL-MYERS/ZIMMER ORTHOPAEDIC SYMPOSIUM

LIMB SALVAGE IN MUSCULOSKELETAL ONCOLOGY

EDITED BY
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Effectiveness of Methyl Methacrylate as a Physical Adjuvant in Local Tumor Control

Opening Remarks

H.-G. Willert

Today, curettage followed by bone cement plugging as surgical treatment of bone tumors is applied mainly to large cystic lesions in the vicinity of the greater joints, such as giant-cell tumors, aneurysmal bone cysts, chondroblastomas, and others.

In order to stabilize defects of the skeleton, bone cement (with or without additional internal fixation) has been used extensively since 1962 in osteolytic metastases and pathologic fractures.[1-6]

In 1968, Wouters[7,8] applied this technique for the first time to a giant-cell tumor, as did Persson[9,10] in 1972. These authors published their results in 1974 and 1984 (Wouters), 1976 (Persson and Wouters) and 1984 (Persson et al.). We have also applied bone cement plugging since 1972, particularly in primary bone tumors and tumorlike lesions that create large osteolytic defects. Unlike other surgeons, we considered cementing a temporary procedure, requiring removal and replacement by bone grafting at a later date, when recurrences are less likely to occur.[11-13] We reported on results for the first time in 1977 and than in 1979 and 1983. Further reports on this topic were given by Vidal et al.,[14] Mandi and Kiss,[15] and Baddeley and Cullen.[16]

From this panel we will hear about the updated experiences of several distinguished centers with this method, among which Johnston and Persson leave the cement plug in place, Camargo and Camargo are using it in connection with polyethylene implants, while Conrad et al., Taminiau and Wouters, and our group removed the cement and grafted the cavity in a second operation (Table 6-1).

The concept of curettage and subsequent bone cement plugging has several advantages: the affected bone as well as the functional capacity of the joint will be preserved, allowing a quick return to active motion and at least partial weight bearing. Radiographic control of the affected site is easy since recurrences or secondary changes are visible early and are relatively easy to localize. In case of a recurrence, curettage and bone cement plugging can be repeated. If desired, autologous bone, which is only available in limited amounts, can be saved for a subsequent, definite grafting. Whether

Table 6-1. Bone Cement Plug Used in Giant-Cell Tumors and Similar Lesions

Author	*Technique First Applied*	*Published*
Vidal et al.	1968	1969
Wouters	1968	1974, 1984
Persson et al.	1972	1976, 1984
Willert et al.	1972	1977, 1979, 1983
Johnston	1973	1985
Mandi et al.	1973	1976
Baddeley et al.	1975	1979
Camargo et al.	1974	1985
Conrad et al.	1979	1985

tumor cells, eventually left behind during curettage, will be devitalized due to the action of cytotoxic monomer or heat released from the polymerizing bone cement is still controversial. Several contributions to this panel will address this question (Conrad et al., Malawer et al., Strube et al., and Wilkins et al.).

However, certain shortcomings of the method should also be mentioned. Regarding the loading capacity, it is hard to predict whether and how long the plugged bone can tolerate full weight bearing over the long term without mechanical failure. This depends substantially on the size and the location of the lesion. We also have to be aware of tissue reactions to the polymethyl methacrylate implant, which will be discussed by Enderle, Strube et al., and Wilkins et al. in this panel. Depending on the mechanical situation, the potential tissue reaction, and the often young age of the patients, the cement plug was usually removed and replaced it by autologous bone after a certain interval.

Finally some investigators (including Wilkins et al.) are afraid of the development of osteoarthrosis when the plug is close to the articular cartilage. In the clinical reports of Conrad et al., Johnston, Persson et al., and our group, only a few observations of secondary osteoarthritis due to bone cement plugging have been noted.

In order to obtain long-lasting good functional results, satisfactory stability, and to avoid local recurrences a perfect surgical technique is required for both curettage and bone cement implantation.

As an alternative to curettage and bone cement plugging, cryosurgery is recommended by Marcove and co-workers. In this panel, Malawer et al. will report on the effect of cryosurgery in a tumor cavity and will compare this with the use of the temporary bone cement plug.

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Clinical Results of the Temporary Acrylic Bone Cement Plug in the Treatment of Bone Tumors: A Multicentric Study

H.-G. Willert

We have found bone cement plugging (BCP) very valuable in the treatment of large osteolytic lesions of bones, especially of lesions that are located adjacent to a joint and that have a marked tendency to recurrence. Since such lesions are relatively rare, however, the experience of a single institution in our country is only limited. We therefore initiated a retrospective multicentric study to which eight departments contributed their material (Table 6-2).

It is in the nature of a retrospective multicentric study that principles of treatment are not always followed as stringently as in a personal series. On the other hand, the efficiency of a method can be tested best by its application under various conditions of clinical practice. To complete the evaluation, we will compare some data from this study with those of our small personal series.

METHOD

The technical procedure for bone cement plugging comprises several steps. It starts with excision of the tumor (or tumorlike lesion) and subsequent filling of the cavity with bone cement. It is of the utmost importance to remove all the tumorous tissue carefully and completely. We recommend not only curetting but also milling the walls of the cavity using a burr. When the bone cement is introduced, the cavity should be as clean and as dry as possible and the bone cement should fill it totally. Sometimes it is better to implant the bone cement in portions. Depending on the mechanical situation, an additional internal fixation can be necessary.

Although the bone cement applied in this way

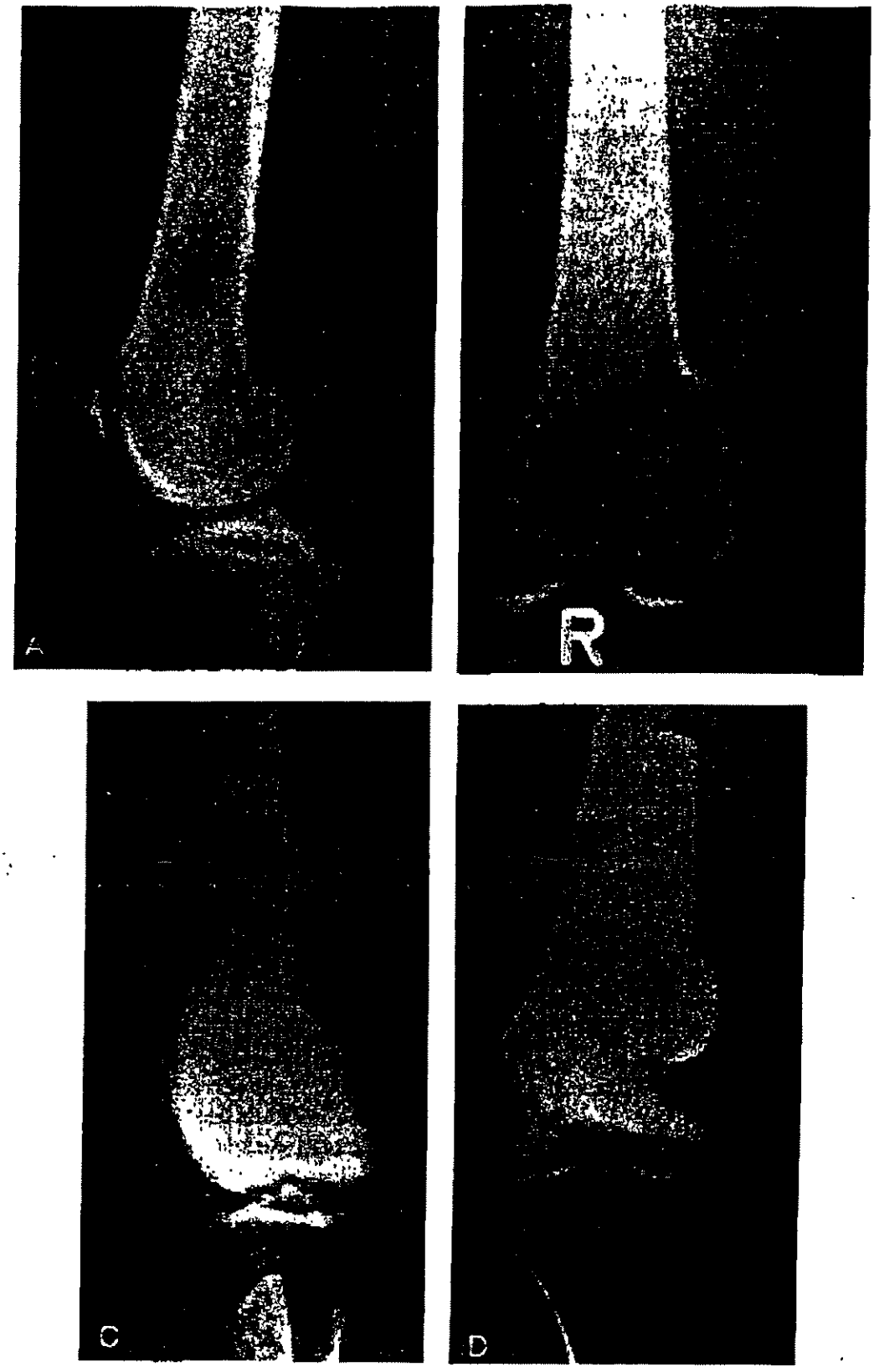


Fig. 6-1. Giant-cell tumor in a 29-year-old woman. **(A,B)** August 1983: The tumor extends far into the popliteal region. **(C,D)** August 1983: Status immediately after curettage, BCP, and internal fixation. *(Figure continues.)*

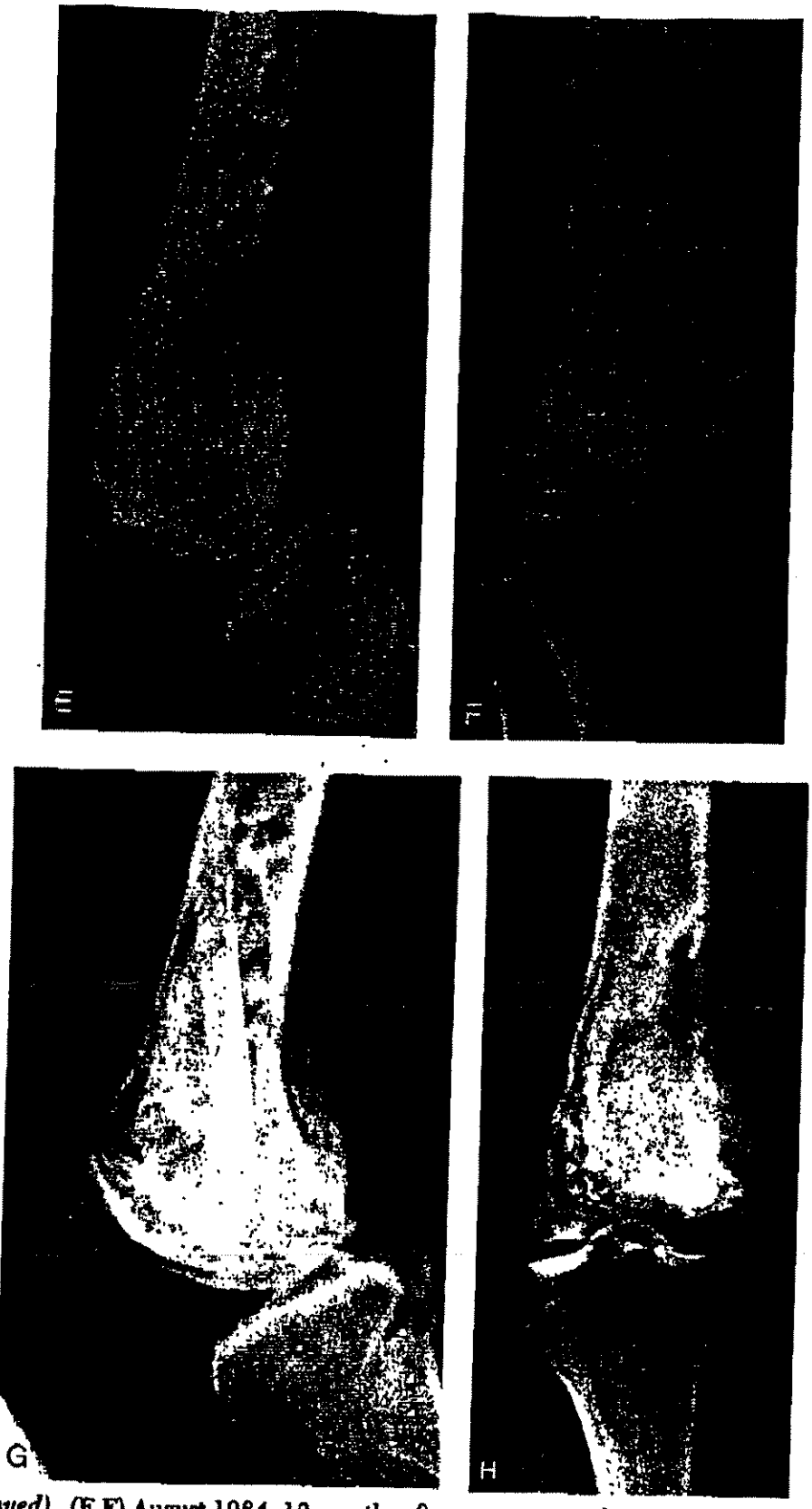


Fig. 6-1 *(Continued).* (E,F) August 1984: 12 months after curettage and BCP. (G,H) September 1985: 8 months after removal of BCP and bone grafting. Patient has been disease-free for 24 months. Functional rating: Good.



Fig. 6-2. Aneurysmal bone cyst in a 14-year-old girl. (A) August 1982: First relapse after curettage and bone grafting. (B) August 1982: Status immediately after curettage and BCP. (C) July 1983: 11 months after BCP. (D) July 1983: Removal of BCP and bone grafting. (E) May 1985: 22 months after bone grafting. Patient has been disease-free for 34 months. Functional rating: Excellent.

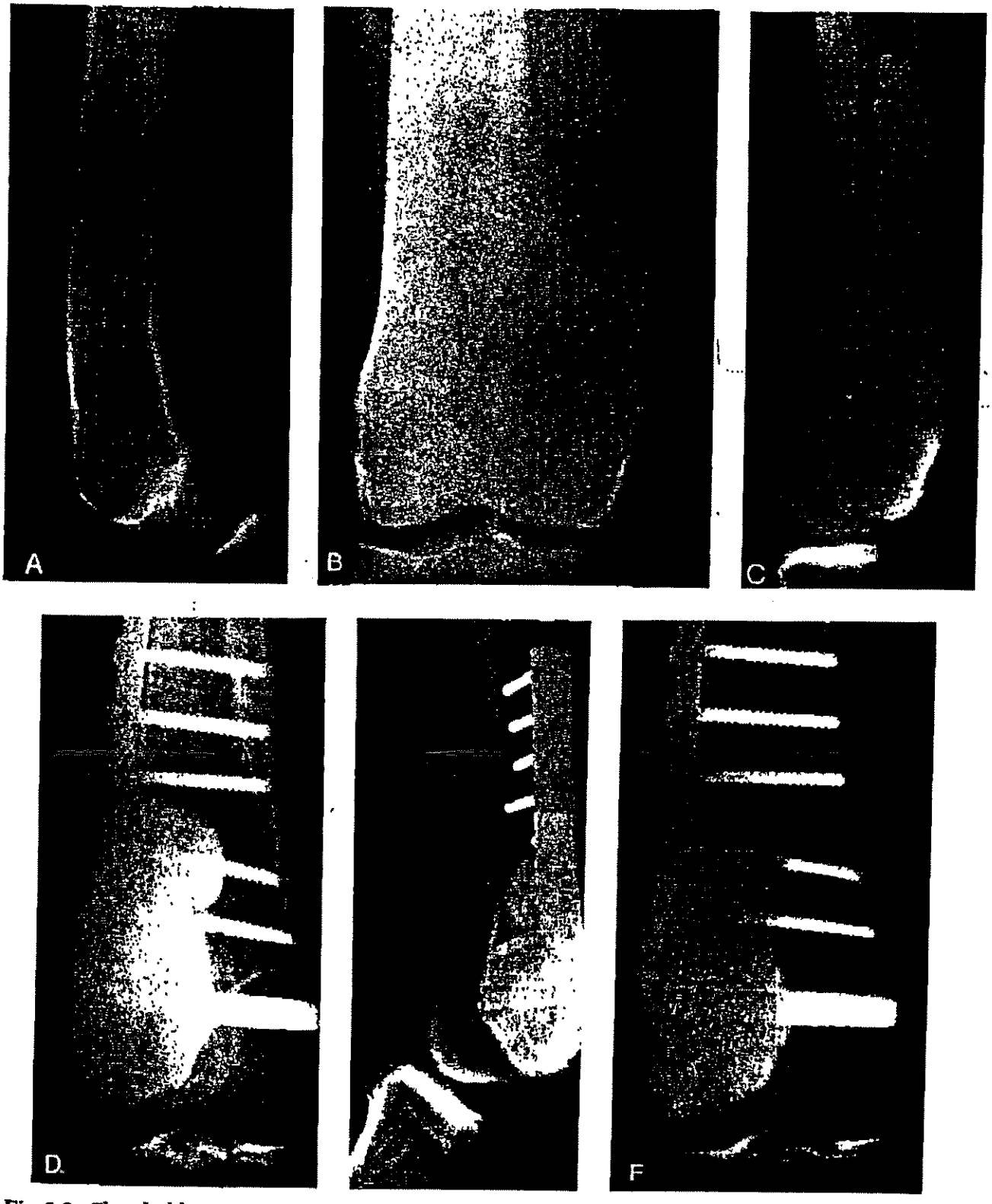
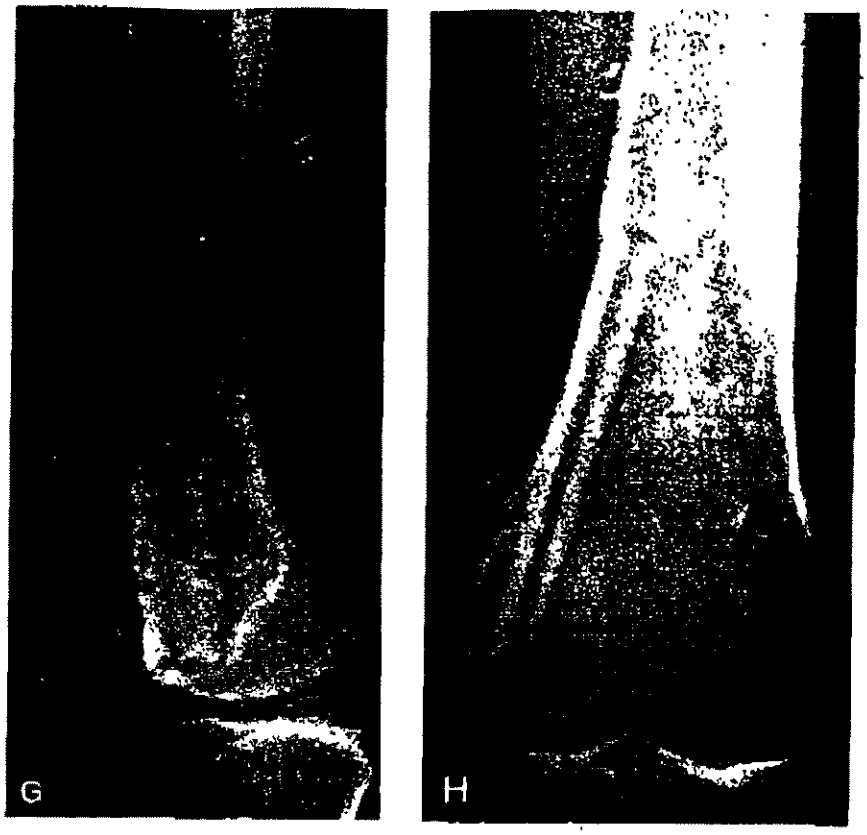


Fig. 6-3. Chondroblastoma in a 19-year-old woman. (A,B) January 1982: Tumor extends anteriorly into the suprapatellar region. (C,D) May 1982: 3 months after curettage, BCP, and internal fixation. (E,F) February 1984: 24 months after curettage, BCP, and internal fixation. *(Figure continues.)*



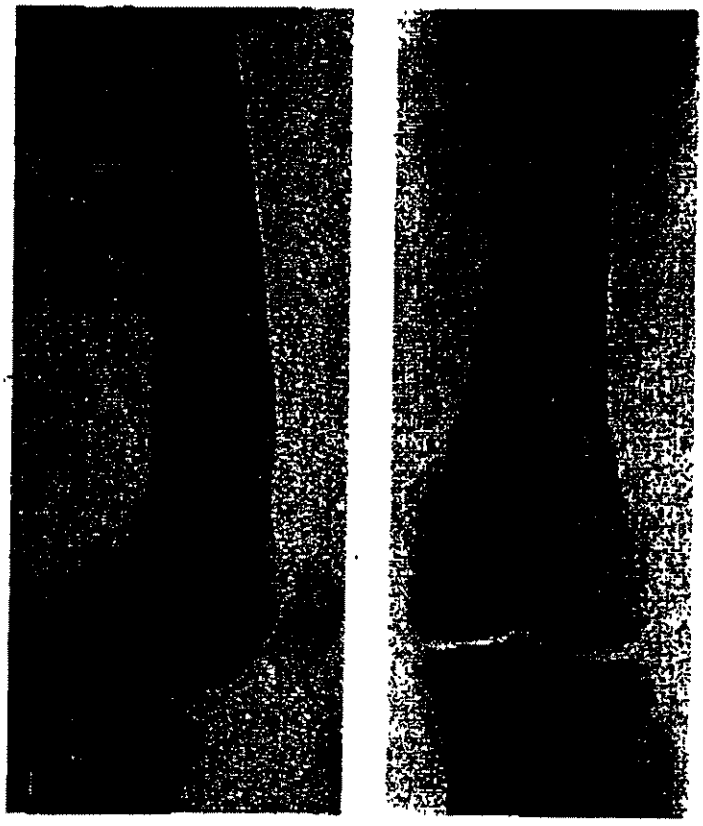


Fig. 6-3 *(Continued)*. **(C,H) March 1984: 1 month after removal of BCP and bone grafting. (I,J) April 1985: 13 months after bone grafting. Disease-free for 39 months. Functional rating: Excellent.**

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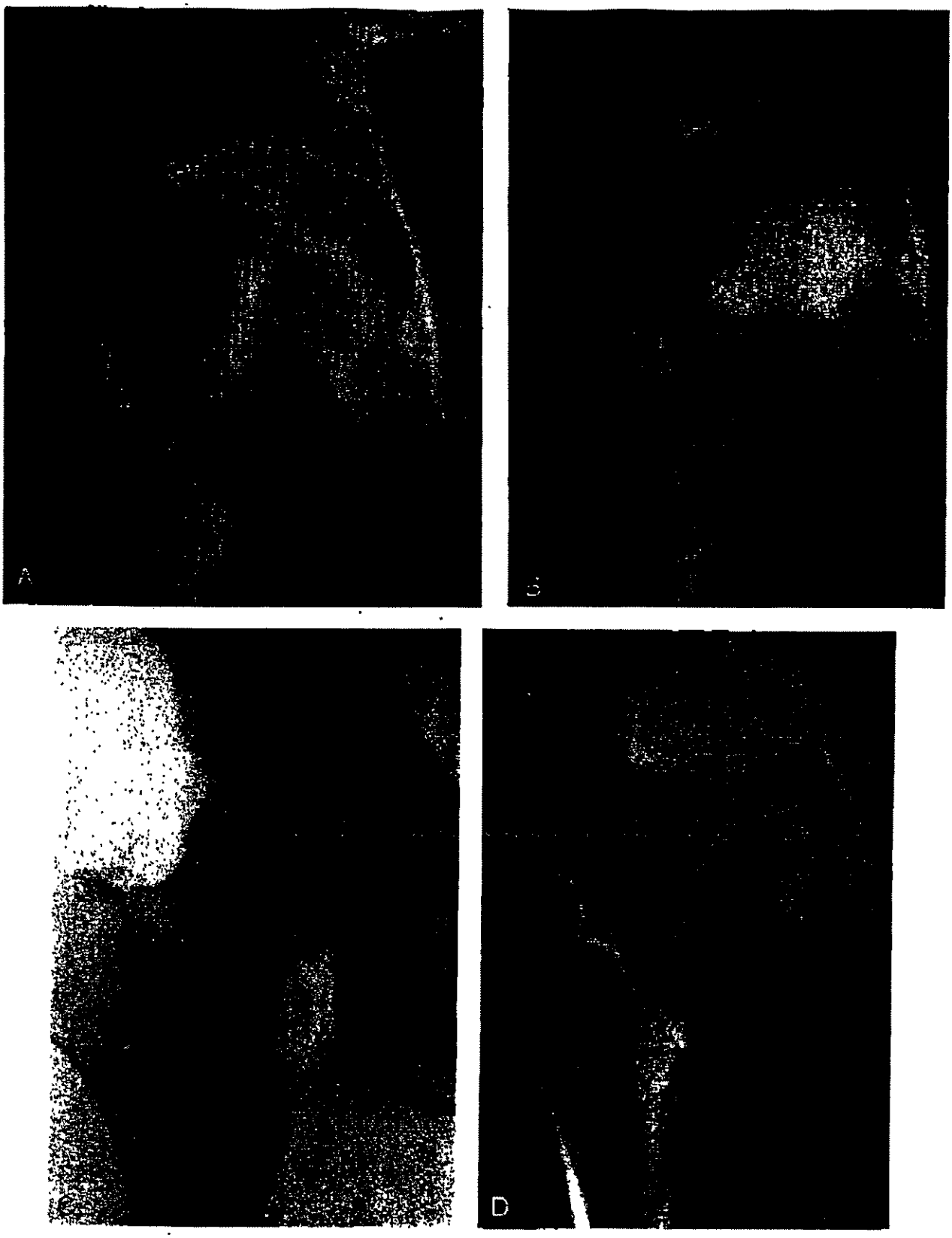


Fig. 6-4. Giant-cell tumor in a 30-year-old man. (A) Appearance in October 1977. (B) February 1978: 4 months after curettage and BCP. (C) November 1978: 1 month after removal of BCP and bone grafting. (D) August 1983: 58 months after bone grafting. Patient has been disease-free for 70 months. Functional rating: Excellent.

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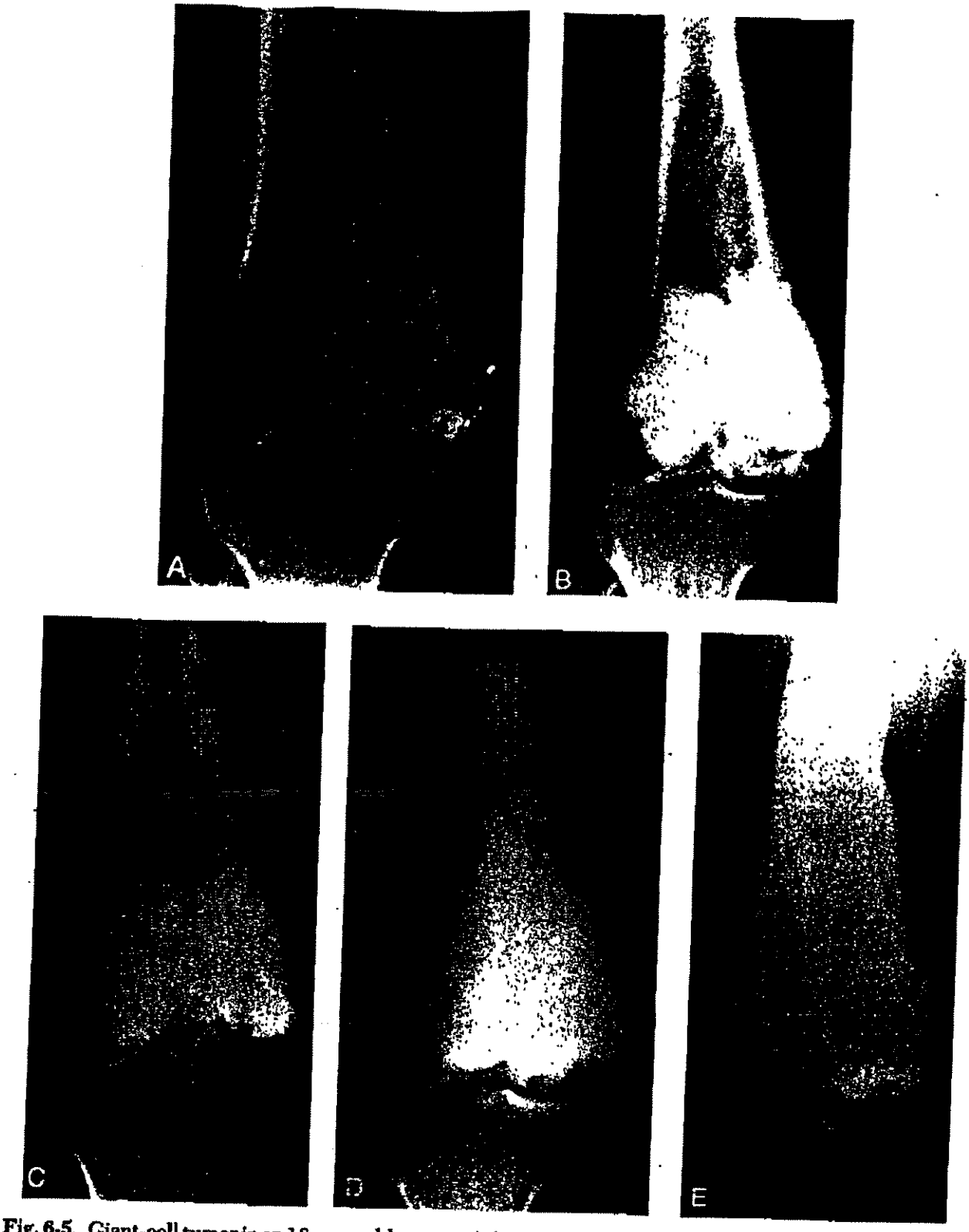


Fig. 6-5. Giant-cell tumor in an 18-year-old woman. (A) May 1981: Second relapse after curettage and bone grafting. (B) August 1981: Incomplete curettage and BCP. (C) October 1981: Progressive bone destruction proximal to BCP. Biopsy (window in lateral cortex) proves presence of giant-cell tumor tissue. (D) October 1981: Repeated complete curettage and BCP. (E) April 1985: Patient has been disease-free for over 42 months. Functional rating: Excellent.

Table 6-2. Contributing Departments and Coauthors: Multicentric BCP Study

Center and Author	*Number of Patients*
Orthopaedic Department "Friedrichsheim," University of Frankfurt, Federal Republic of Germany L. Hovi and L. Zichner	21
Orthopaedic Department, University of Innsbruck, Austria W. Russe	5
Orthopaedic Department, University of Göttingen, Federal Republic of Germany A. Enderle and H.-G. Willert	4
Orthopaedic Hospital, Göttingen, Federal Republic of Germany R. Braig and M. Spranger	3
Department of Accident Surgery, University of Mainz, Federal Republic of Germany H.-D. Strube and D. Komitowski	2
Orthopaedic Department University of Tübingen, Federal Republic of Germany J. Gekeler	2
Orthopaedic Department, St. Josef-Hospital, Troisdorf, Federal Republic of Germany P. Puls	1
Orthopaedic Hospital, Vollmarstein, Federal Republic of Germany W. Becker	1
Total	39

seems to behave rather inertly, we still tend to remove it in younger patients after a follow-up period of up to 2 years and to refill the cavity with bone, if possible with autografts (Figs. 6-1 to 6-5). In case of a recurrence a repeated excision, again followed by implantation of bone cement, can be employed. More radical surgical procedures, such as en bloc resection or amputation, also have to be taken into consideration, particularly in more aggressive lesions. Removal of the bone cement plug is easy, if one proceeds step by step, splitting the acrylic mass using a chisel or saw. The membrane of connective tissue that usually develops at the bone–cement interface should be removed with another careful curettage. To increase mechanical stability, internal fixation in addition to bone grafting is sometimes necessary. Histologic investigation of the connective tissue membrane removed will show even small recurrences of tumor growths in the walls of the former lesion.

MATERIAL

A total of 39 lesions treated with BCP are included in this multicentric study. If we count from the first application of curettage and BCP, the follow-up period is close to 2 years and longer for 29 lesions (group A, range of 22–114 and an average of 55 months) and shorter than 2 years for 10 lesions (group B, range of 4–20, average of 16 months) (Table 6-3). In 14 cases the bone cement was removed and replaced by bone grafting after an average of 13 months (range, 1–26 months), in 2 cases the plug was only removed but not replaced, and in 10 cases the bone cement has not been removed and is still in place. In one case a resection–arthrodesis and in two an amputation became necessary. The lesions treated by curettage and BCP included 21 giant-cell tumors, 7 aneurysmal bone cysts, 3 solitary bone cysts, 2 fibromas, 2 unilocular fibrous dysplasias, 2 chondroblastomas, 1 osteosarcoma, and 1 chondromyxoid fibroma. Fifteen of the 39 lesions (38%) had already relapsed one to three times prior to the treatment by curettage and BCP. In these 15 cases, BCP has been applied to recurrences (Tables 6-4, 6-5).

The diagnosis of one aneurysmal bone cyst was changed by the pathologist, after it recurred several times, to malignant giant-cell tumor, stage IA.

The preferential site of the osteolytic lesions treated was around the knee (21), followed by the proximal femur (5), the distal tibia (4), the distal radius (3), the proximal humerus (2), the pelvis (2), the proximal ulna (1), and the distal fibula (1).

Table 6-3. Follow-Up Since BCP (months)

	Total	*Group A (>2 years)*	*Group B (<2 years)*
Number	39	29	10
Range	4–114	22–114	4–20
Average	45	55	16

Table 6-4. Proportion of Lesions that Relapsed before BCP, According to Histologic Diagnosis

	Total		*Group A*		*Group B*	
	N	*Percent Relapsed*	*N*	*Percent Relapsed*	*N*	*Percent Relapsed*
Giant-cell tumor	21	8	15	5	6	3
Aneurysmal bone cyst*	7	4	7	4	—	—
Solitary bone cyst	3	1	2	—	1	1
Fibrous dysplasia	2	—	1	—	1	—
Chondroblastoma	2	1	1	—	1	1
Fibroma	2	1	2	1	—	—
Chondromyxoid fibroma	1	—	—	—	1	—
Osteosarcoma	1	—	1	—	—	—
Totals	39	15	29	10	10	5

* One aneurysmal bone cyst progressed to a giant-cell tumor, stage IA.

Table 6-5. Histologic Diagnosis of Lesions that Relapsed before BCP

	Relapses Prior to BCP				*Recurrences After BCP*			
	1	*2*	*3*	*Total*	*1*	*2*	*3*	*Total*
Giant-cell tumor	3	4	1		1			
Aneurysmal bone cyst	2	1	1				1*	
Fibroma	1				1			
Solitary bone cyst	1							
Chondroblastoma	1							
	8	5	2	15	2		1	3

* Change of histopathologic diagnosis to malignant giant-cell tumor, stage IA.

RESULTS

At the time of their respective follow-up examinations, 38 of 39 patients were disease-free over a period of 3–114 months. In 25 of 29 group A (follow-up 2 years) patients (86%) this disease-free interval was longer than close to 2 years.

Recurrences

Eight of the 39 lesions (20.5%) recurred between 1 and 43 months (average, 14 months) after the treatment with curettage and BCP. Four of them recurred once, three twice, and one three times. The recurring lesions were four giant-cell tumors, two aneurysmal bone cysts, one fibroma, and the one osteosarcoma (Table 6-6). The recurrences occurred in 5 of 24 (20.8%) primary lesions in which the first treatment was curettage and BCP and in 3 of 15 (again 20%) lesions treated by other methods that relapsed prior to BCP (Table 6-5). All lesions that recurred had been staged before BCP as 3 or higher agressive (IA, IB, and IIB). The surgical procedure has been either a marginal or an intralesional removal. The management of recurrences of three giant-cell tumors, one aneurysmal bone cyst, and one fibroma consisted of repeated curettage and BCP as well as curettage and bone grafting.

In one aneurysmal bone cyst a resection–arthrodesis (Juvaraplasty) was carried out after the third recurrence. The affected leg was amputated immediately after the first recurrence of the osteosarcoma.

One patient with a malignant giant-cell tumor stage IB died 13 months after the first treatment by

Table 6-6. Recurrences after BCP

Number of Cases	Number of Recurrences	Percent	Histologic Diagnosis	Recurrences 1	2	3
21	4	19	Giant cell tumor	2	2	
7	2	28	Aneurysmal bone cyst		1	1
2	1	50	Fibroma	1		
1	1	100	Osteosarcoma	1		
3	0	—	Solitary bone cyst			
2	0	—	Fibrous dysplasia			
2	0	—	Chondroblastoma			
1	0	—	Chondromyxoid fibroma			
Total 39	8	20.5				

curettage and BCP. A first recurrence was treated by a repeated curettage and BCP. After a second recurrence an amputation was carried out, but the patient developed lung metastases.

Seven of the eight patients with recurrent lesions, including the one with osteosarcoma, were still disease-free at the time of follow-up examination, three of them for longer than 2 years (Table 6-7).

A careful analysis of the radiographs revealed that in at least five of the eight recurrences the initial removal of the lesion has to be considered incomplete (Fig. 6-5). It may be of interest that two of the three giant-cell tumors of the distal radius have recurred (Table 6-8).

Infections

Of the 39 BCPs, 2 (approximately 5%) became infected. This was apparent in one case at 5 months and in the other at 10 months after surgery. In both cases the bone cement was removed and the infection could be controlled by local irrigation. Healing occurred with no symptoms (Table 6-9).

Table 6-7. Management and Result of Eight Recurrences after BCP

Lesion	Recurrence after BCP (months)	Management	Result: Disease-Free (months)	Result: Clinical Evaluation	Result: Device Evaluation
GCT[a]	6	Curettage + BCP	42	Excellent	Excellent
GCT	8	Curettage + BCP	57	Excellent	Good
Fibrosarcoma[a]	25	Curettage + BCP	3	Excellent	Excellent
Osteosarcoma	22	Amputation	72	Good	—
GCT[b]	2,6	Curettage + BCP Amputation	Died at 13 months	Poor	—
GCT	12,23	Curettage + bone graft Curettage + BCP	9	Good	Good
Aneurysmal bone cyst	12,43	Curettage + BCP Curettage + bone graft	6	Good	Good
Aneurysmal bone cyst[a]	1,11,16	Curettage + bone graft Curettage + BCP Resection–arthrodesis (Juvaraplasty)	8	Fair	Poor[c]

[a] Recurrent lesion prior to BCP.
[b] Stage IB.
[c] No active movement; required removal.

Table 6-8. Site and Quality of Curettage with BCP in Recurrent Lesions

Histologic Diagnosis	*Recurrence After Primary BCP (months)*	*Site*	*Quality of Curettage and BCP*
Giant-cell tumor	6	Distal femur	Incomplete
Giant-cell tumor	8	Distal radius	Incomplete
Giant-cell tumor	2	Distal femur	Incomplete
Giant-cell carcoma	6		
Giant-cell tumor	12 23	Distal radius	Sufficient
Aneurysmal bone cyst	12 43	Distal femur	Incomplete
Aneurysmal bone cyst	1 11 16	Proximal tibia	?
Fibroma	25	Distal femur	Incomplete
Osteosarcoma	22	Distal femur	Sufficient

Table 6-9. Management and Results of Two Infections after BCP

Histologic Diagnosis	*Infection After Primary BCP (months)*	*Management*	*Result*		
			Disease-Free (months)	*Clinical Evaluation*	*Device Evaluation*
Aneurysmal bone cyst	5	BCP removed Irrigation BCP removed Irrigation	40	Good	Fair*
Giant-cell tumor	10	Curettage + BCP	29	Excellent	Good
		Removal of BCP and bone graft			

* Required removal.

Osteoarthrosis

In 23 patients with lesions located subchondral to a joint, assessment of the course by reviewing the radiographs was possible. Radiographic signs of osteoarthrosis were present in eight cases with a mean follow-up of 56 months. In these, defects of the subchondral bone were present in two lesions, and in another one osteoarthrosis already existed at the time of BCP. In 15 cases with a mean follow-up of 38 months, osteoarthrosis was absent (Table 6-10).

Table 6-10. Osteoarthrosis (OA) in 23 Lesions Subchondral to Joint

	Number	*Mean Follow-Up (months)*	*Remarks*
OA Present	8	56	Two defects of subchondral bone
OA Absent	15	38	

Twelve lesions were located far from the joint.
No information on location was available for four lesions.

Table 6-11. Evaluation of BCP

Rating	*Functional*	*Device*
Excellent	25	10
Good	11	25
Fair	2	3
Poor	1	1
Total	39	39

Table 6-12. Functional Results in Cases with and without Osteoarthrosis (OA)

		Functional Rating			
	Total	*Excellent*	*Good*	*Fair*	*Poor*
OA Present	8	6	1	1	
OA Absent	15	10	4		1

FUNCTIONAL EVALUATION

The functional evaluation of BCP showed Excellent results in 25, Good in 11, Fair in 2, and Poor in 1 patient (Table 6-11).

The outcome was Poor in the patient who died from lung metastases after repeated recurrences. One lesion of the proximal humerus was rated as Fair because of osteoarthrosis and weakness of the movements of the shoulder joint. The other Fair result was a repeatedly recurring aneurysmal bone cyst of the proximal tibia, the diagnosis of which has been changed to giant-cell tumor. But the Fair rating concerned only the BCP. In this patient a resection–arthrodesis was carried out, the result of which was Excellent since only the motion of the knee was lost. Reasons for a Good rating were mostly minor restrictions of motion, stability, and/or emotional acceptance.

Even among the lesions that recurred, the results could be rated three times as Excellent and three times as Good (Table 6-7).

Manifest osteoarthrosis does not seem to affect the final outcome unfavorably. Six of the eight patients with osteoarthrosis were rated Excellent, one Good, and only one Fair (Table 6-12).

The rating of the device clearly showed less favorable results. Only 10 cases could be rated as Excellent, 25 were Good, 3 Fair, and 1 Poor. The reason for this was most often restricted weight bearing for several weeks, together with a mild tissue reaction.

In the relatively small series treated personally

Table 6-13. Results of Author's Personal Series

Histologic Diagnosis	*Site*	*Follow-Up BCP (months)*	*Recurrence/ Infection (months after BCP)*	*BCP Removed Bone Graft (months after BCP)*	*Disease-Free (months)*	*Clinical Evaluation*	*Device Evaluation*
GCT	Distal femur	114	—	14	114	Excellent	Good
GCT	Proximal tibia	100	—	11	100	Excellent	Good
GCT	Proximal femur	70	—	12	70	Excellent	Good
GCT	Distal femur	57	—	16	57	Excellent	Good
GCT (recurrence)	Distal femur	22	—	17	20	Good	Good
ABC (3rd recurrence)	Distal tibia	85	—	14	85	Good	Good
ABC	Distal femur	49	Recurrence 2 + 43	6	6	Good	Good
ABC	Proximal femur	45	Infection 5	5	40	Good	Fair
ABC (recurrence)	Proximal tibia	34	—	11	34	Excellent	Good
Chondroblastoma	Distal femur	39	—	24	39	Excellent	Good
Solitary bone cyst	Proximal humerus	85	—	—	85	Good	Good
Solitary bone cyst	Pelvis	82	—	8	82	Excellent	Good
Totals 12		65	1 Recurrence (8%)	11 (92%)	60	7 Excellent	11 Good
			1 Infection (8%)			5 Good	1 Fair

CCT, giant-cell tumor; ABC, aneurysmal bone cyst.

by the author, 12 cases were evaluated over a mean period of 65 months (range, 22–114). Only one of them (8%) developed a recurrence but another one (8%) became infected. Further details are shown in Table 6-13.

DISCUSSION

The overall results of BCP in this multicentric study are satisfying. All patients except one were disease-free at the time of follow-up-examination; 25 were followed up for about 2 years or longer.

The recurrence rate of 20.5% after BCP is relatively low, compared to reports from the literature with giant-cell tumors, aneurysmal bone cysts, and others. Yet the incidence of recurrences among lesions treated by other methods and that relapsed prior to BCP was not higher than among the primary lesions in which curettage and BCP constituted the first operation. This can be regarded as a Good result, particularly one considers that 38% of all the lesions included in this study had already relapsed prior to BCP treatment.

Most of the recurrences could be controlled by repeat curettage and BCP.

There is no doubt that curettage creates only a marginal or intralesional surgical margin. That is why the greatest attention must be paid to a painstaking excision of the lesion and aggressive cleaning of the walls, to remove the tumorous tissue as completely as possible. Likewise the cement plug must fill every recess of the cavity entirely. Though we observed devitalization of the tissue adjacent to the BCP, one cannot rely on this effect and therefore should not neglect a careful mechanical scraping. In five of the eight recurrences in the multicentric study the removal of the lesion was incomplete, as could be proved on the radiographs. In contrast to this, in our personal series of 12 cases in which we were anxious to remove every residual tumorous tissue, we experienced only 1 recurrence of a giant-cell tumor.

For the treatment of malignant tumors, however, curettage and BCP seem to be clearly unsuitable and cannot be recommended.

Up to now we have personally preferred to remove the acrylic bone cement, as we hesitate to leave a foreign material permanently in the body, particularly in younger people. We have kept to this procedure though we found an only relatively moderate reaction of the surrounding tissue to the BCP compared with the tissue reaction to acrylic bone cement used in artificial joint replacement. In lesions such as giant-cell tumors, aneurysmal bone cysts, and chondroblastomas, we consider it sufficient to leave the BCP in place for about 28 months. All except one of the recurrences in our study appeared within this length of time.

Symptoms of osteoarthrosis were found in 34% of patients with subchondral bone lesions in the vicinity of a joint. Defects of the subchondral bone lamella created during the curettage or the plug-removing procedure seem to promote the development of osteoarthrosis.

The cases showing manifest osteoarthrosis were evaluated longer than those with no osteoarthrosis. This means that osteoarthrosis may develop sooner or later in patients lacking signs of joint deterioration at the time of examination.

The functional evaluation was influenced only a little or not at all by the presence of osteoarthrosis; most of these patients had Excellent results.

In summary, temporary bone cement plugging of large osteolytic cavities in bone tumors and tumor-like lesions has proven to be a good method. Its advantage is that the mobility of the joint as well as the continuity and stability of the bone can be preserved, the follow-up is easy using x-ray examination and, if necessary, further therapeutic measures are still possible. To prevent recurrences the curettage has to be done as carefully as possible and should be followed by milling the walls of the cavity. We recommend removing the BCP and the connective tissue formed at the bone–cement interface and refilling the cavity with autologous bone grafts.

Experimental Studies of the Treatment of Malignant Tumors with Bone Cement

Hans-Dietmar Strube and Dmitri Komitowski

The defect left after resection of malignant bone tumors is sometimes repaired by filling it with bone cement, either temporarily or permanently, and stabilizing it further with plates. In addition to providing early functional stabilization, this "combined osteosynthesis" method may have the advantage that the cement itself destroys remaining, relapse-causing malignant cells. As it polymerizes, bone cement releases heat and cytotoxic monomers. In sound bone and soft tissue this effect is usually disadvantageous, but it may be desirable when malignant tumor cells exist.

Whether this effect might be clinically valuable needed to be determined in animal experiments. In vitro investigations using tissue cultures on hardened cement were also indicated. We undertook both kinds of investigations, looking for long-term effects that might damage tumor cells.

MATERIALS AND METHODS

In Vivo Experiments

We needed a model of bone sarcomas that corresponded morphologically and biologically to human sarcomas. For better observation of the process, we also wanted a model that would grow slowly, stay at the site of its formation, and not metastasize uncontrollably and prematurely.

The experimental animals had to be suitable for clinical, radiographic, and histologic investigations comparable to those of human medicine. Most of all, operations such as resection, cement implantation, and functional stabilization that are practicable on the human skeleton had to be possible and tolerable. The femur of 3–5-month-old rabbits proved to be suitable for the experimental model.

To produce sarcomas, we used 7,12-dimethylbenz(*a*)-anthracene (DMBA), a carcinogen of the group of polyaromates often used to induce experimental tumors.[2,3]

To produce bone sarcomas with the desired predefinable localization, the carcinogen was coupled to heated and liquefied gelatine as vehicle. After being cooled and hardened, the particles were incorporated into the medullary canal of the femur through boreholes (Fig. 6-6).

There the gelatin induces a reactive myelofibrosis. The carcinogen is fixed in a "biologic capsule" and cannot be washed off. It can therefore work directly where applied after reduction of the vehicle (Fig. 6-7). For polymethyl methacrylate bone cement, we used Palacos R.

In Vitro Experiments

We laid small discs of the same cement into special tissue cultures and investigated the growth and reproduction of the cells by scanning electron microscopy. As well as these tests with already hardened cement, we studied the effect of the liquid component of methyl methacrylate on special murine lymphoma cells.[4]

RESULTS

In Vivo Experiments

With the technique described, 10 of 25 animals developed after 2–4 months, radiologically discernible tumors that grew to their full size within

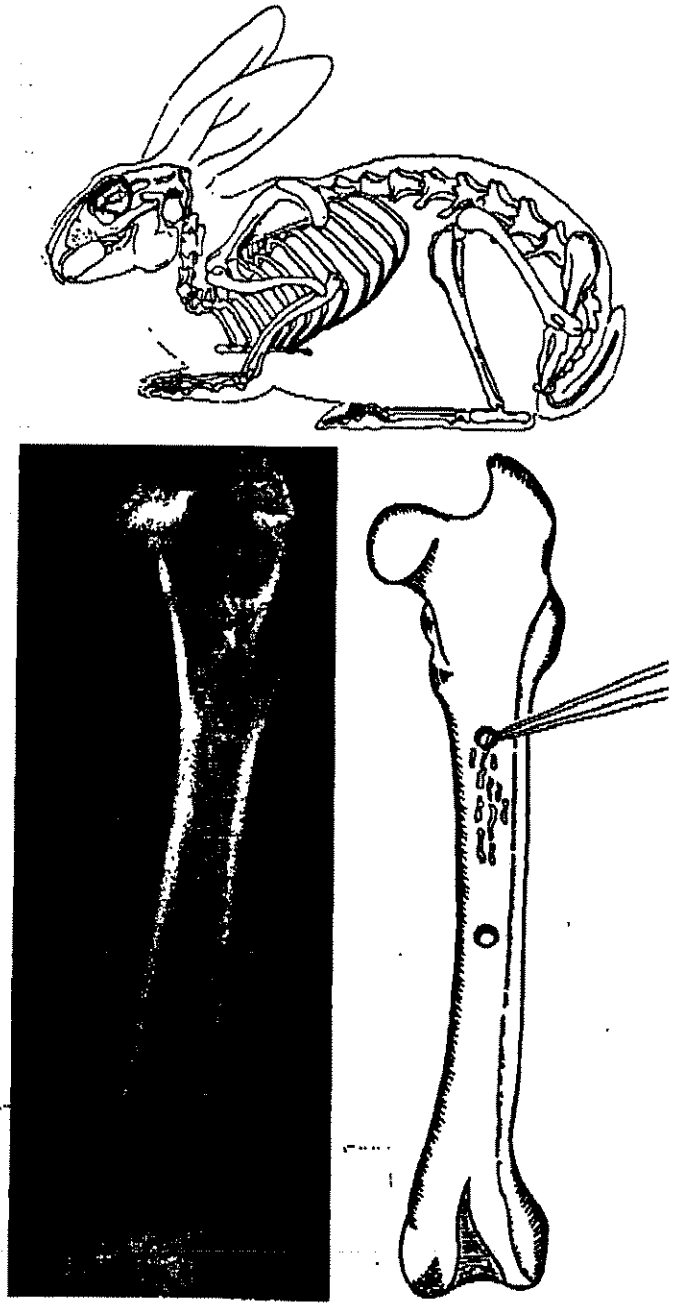


Fig. 6-6. Diagram of a rabbit skeleton, and drawing and radiograph of a femur with 2 mm drill holes and incorporation of gelatin vehicle substances with carcinogen.

12–14 months. As in humans, pathologic fractures were only found in far-advanced stages. Metastases outside the femur were not observed. The clinical and radiologic development of sarcomas, the macroscopic appearance of the tumors, and their morphology showed a far-reaching conformity with



Fig. 6-7. Sketch of the "biologic capsule" with reactive myelofibrosis round the hardened gelatin particles with DMBA.

comparable human tumors (Fig. 6-8). Altogether eight osteogenic sarcomas, one fibrosarcoma, and one chondrosarcoma developed. As radiologic evidence we found three stages of tumor development:

1. At the earliest, (sixth to eighth week) an intraosseous growth, issuing from the place of carcinogen implantation with fine-spotted osteolysis (Fig. 6-9A).
2. Periostal reactions, beginning after about 6 months (Fig. 6-9B).
3. After about 1 year the tumor followed parosteal growth with partly diffuse extent and sometimes pathologic fractures (Fig. 6-9C,D).

The scintigram and computed tomogram revealed distinct enrichment of activities and a filling of the medullary cavity of the femur (Fig. 6-10).

Depending on the general situation and the local tumor growth the subsequent cement implantation was done either with or without additional stabilization by metal plate and screws. After partial tumor resection the defect was filled with bone cement and, if necessary, a small one-third-tubular plate and four screws were applied (Fig. 6-11).

Just as in the tumor-free experimental animals, the histologic examinations 24 hours and 4 and 10 weeks after cement implantation showed tissue necrosis in the immediate area of cement contact. The sarcomatous tissue is bounded by necrotic areas (Fig. 6-12). We found the following temporarily modified areas of cement reaction (Fig. 6-13).