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Intra-operative radiation therapy for osteosarcoma in the extremities

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Abstract The outcome following intra-operative radiation therapy in the treatment of osteosarcoma in the extremity in 33 patients was evaluated for oncological and functional results. Local recurrence occurred in seven cases, six of which were in a non-irradiated region, indicating inappropriate planning of the radiation field. Twenty-one patients underwent either prosthetic replacement (14) or amputation (7). Irradiated tumours were left in situ in the remaining 12 patients. In this latter group no degenerative joint changes were observed radiologically. Twenty-six patients experienced local complications, of which fracture of the irradiated bone was the most significant. Associated intramedullary nailing showed encouraging results in preventing fracture. Although IORT is effective for the local control of osteosarcoma in extremities, critical patient selection and improvements of treatment protocol are required in order to obtain a satisfactory outcome.

Résumé On a examiné les résultats oncologiques et fonctionnels de 33 patients ayant reçu une radiothérapie peropératoire pour un ostéosarcome d'une extrémité. Sur les sept cas de récidive locale identifiés, six se situaient dans une région apparemment non irradiée, ce qui indique que la défaillance locale pourrait être due à un défaut de détermination du territoire irradié. Sur les 33 patients, 14 ont reçu une endoprothése et 7 été amputés après la radiothérapie. Les tumeurs irradiées ont été laissées in situ chez les 12 patients restants. Dans ce dernier groupe, l'examen radiologique n'a révélé aucune dégénérescence au niveau des articulations. Des complications locales ont été observées chez 26 patients sur 33. La complication la plus problématique était la fracture de l'os irradié. La consolidation par enclouage médullaire a donné des résultats encourageants pour la prévention des fractures. Bien que la radiothérapie peropératoire soit efficace pour la maitrise locale de l'ostéosarcome des extrémités, la sélection judicieuse des patients et l'amélioration de la procédure sont nécessaires pour obtenir un membre fonctionnel à long terme.

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Introduction

Most osteosarcomas in extremities are now treated by limb-saving procedures [6, 14, 17, 22]. These procedures involve resection of the bony lesion with a wide margin of soft tissue and reconstruction by cadaver allogenic grafts or prostheses [2, 4, 5, 7, 10, 15, 23, 25, 27]. Some authors report attempted reimplantation of the affected bone after extracorporeal treatment as soaking in ethanol [19], autoclaving [3, 10], or irradiation [24]. Each method has some advantages but the long term oncologic and functional outcomes have yet to be evaluated.

Sine 1978, we have used intra-operative radiation therapy (IORT) for the treatment of osteosarcoma. IORT was first established as a treatment modality for locally advanced tumours [1], and its use in the treatment of osteosarcoma was described by Abe and Yamamuro [26]. Osteosarcoma is one of the most radioresistant tumours. IORT, however, uses high-dose single irradiation, and total necrosis of irradiated bone has been confirmed histologically [13,16]. In this report we reviewed the clinical

Table 1 Summarized data on 33 patients treated with IORT for osteosarcoma. *gr* group, *rad. length* radiation length, *add. local surgery* additional local surgery, *M* male, *F* female, *DF* distal femur, *MF* midshaft femur, *PT* proximal tibia, *PH* proximal humerus, *linear acc.* linear accelerator, *AP* antero-posterior, *EP* endoprosthesis, *AMP* amputation, *FR* fracture repair, *PN* preventive nailing, *RF* rotation flap, *ATL* achilles tendon lengthening, *DOD* dead of disease, *DOOC* dead of other causes, *AWD* alive with disease, *NED* no evidence of disease, *CDF* continuous disease-free, *gr. A* IORT as a local adjuvant therapy, *gr. B* IORT as a definitive local treatment

No.	Gr.	Age	Sex	Site	Subtype	Radiation	Dose (Gy)	Rad. length (mm)	Resection (if any, mm)	Fracture (mo.)	Recurrence (mo.)	Metastasis (mo.)	Add. local surgery (mo.)	Follow-up (mo.)	Final local status
1	A	13	F	DF	conventional	electrons AP	50	110	130	–	–	+(7)	EP(2)	NED(222)	endoprosthesis
2	A	53	F	DF	conventional	electrons AP	50	240		–	–	+(7)	none	DOD(9)	IORT only
3	A	15	M	PT	conventional, fibroblastic	electrons AP	45	130	130	–	–	+(9)	EP(10)	DOD(21)	endoprosthesis
4	A	17	M	DF	conventional	electrons AP	50	120	150	–	+(12)	+(3)	EP(6)	DOD(15)	endoprosthesis
5	A	15	M	DF	conventional	electrons AP+bilat.	60	180	190	–	–	+(12)	EP(4)	DOD(24)	endoprosthesis
6	A	20	M	DF	conventional, osteoblastic	electrons AP+bilat.	50	140	150	–	–	–	EP(2)	CDF(191)	endoprosthesis
7	A	21	M	PT	conventional	electrons AP+bilat.	50	200		–	–	+(2)	AMP(3)	DOD(28)	amputated
8	A	13	M	PT	conventional	electrons AP+bilat.	45	200		–	–	+(10)	AMP(10)	DOD(40)	amputated
9	A	11	M	DF	conventional, osteoblastic	electrons bilateral	50	200		+(11)	+(4)	+(3)	none	DOD(15)	IORT only pseudoarthorosis
10	A	17	M	DF	conventional, osteoblastic	electrons bilateral	50	180	200	–	–	+(106)	EP(5) AMP(63)	NED(182)	amputated
11	A	12	F	DF	conventional, osteoblastic	electrons bilateral	50	200		–	–	+(4)	none	DOD(16)	IORT only
12	A	15	M	DF	conventional, osteoblastic	electrons bilateral	50	200	200	–	–	+(5)	EP(3)	DOD(7)	endoprosthesis
13	B	12	F	PT	conventional, fibroblastic	electrons bilateral	50	220	50	+(19)	–	–	FR(31) EP(65)	CDF(147)	endoprosthesis
14	B	11	F	DF	conventional, osteoblastic	electrons bilateral	50	190		+(35)	+(9)	+(152)	AMP(111)	AWD(152)	amputated
15	B	15	M	PT	conventional, osteoblastic	electrons bilateral	50	150		–	–	+(5)	none	DOD(22)	IORT only
16	B	12	F	PT	conventional, osteoblastic	electrons bilateral	55	210		–	+(27)	+(7)	RF(13)	DOD(31)	IORT only
17	B	12	M	PH	conventional, osteoblastic	electrons AP	60	190		+(3)	–	–	none	CDF(122)	IORT only pseudoarthrosis
18	B	6	M	DF MF	conventional, fibroblastic	electrons bilateral	50	200		+(3)	–	–	FR(5)) AMP(72	CDF(127)	amputated
19	B	11	M	PT	conventional, small cell	electrons bilateral	50	210		+(17)	–	–	FR(18) AMP(38)	CDF(130)	amputated
20	B	15	M	PT	conventional, osteoblastic	X-rays bilateral	55	250	70	+(12)	–	–	EP(45)	CDF(110)	endoprosthesis
21	B	13	M	PT	conventional, osteoblastic	X-rays bilateral	50	200		+(2)	–	–	FR(33)) AMP(50	CDF(118)	amputated
22	B	13	M	DF	conventional	X-rays bilateral	60	170		+(2)	–	–	FR(4) AMP(38)	CDF(110)	amputated
23	B	20	M	DF	conventional, osteoblastic	X-rays bilateral	45	260	240	already fractured	–	+(2)	EP(4)	DOD(13)	endoprosthesis

Table 1 (continued)

No.	Gr.	Age	Sex	Site	Subtype	Radiation	Dose (Gy)	Rad. length (mm)	Resection (if any, mm)	Fracture (mo.)	Recurrence (mo.)	Metastasis (mo.)	Add. local surgery (mo.)	Follow-up (mo.)	Final local status
24	B	17	M	DF MF	conventional, chondroblastic	X-rays bilateral	55	350		–	–	+(17)	PN(8) 2nd IORT(23)	AWD(109)	nailed
25	B	25	F	DF MF	high-grade surface	X-rays bilateral	60	280		–	+(29)	+(31)	PN(4)	DOD(51)	nailed
26	B	11	M	DF	conventional	X-rays bilateral	55	210		+(12)	–	+(12)	none	DOD(18)	IORT only pseudoarthrosis
27	B	16	M	PT	conventional, osteoblastic	X-rays bilateral	55	230	100	+(4)	–	–	EP(9) ATL(16)	CDF(75)	endoprosthesis
28	B	17	M	DF	conventional	electrons bilateral	60	190	90	+(11)	–	–	EP(23) 2nd EP (50)	CDF(70)	endoprosthesis
29	B	13	F	PT	conventional, osteoblastic	X-rays bilateral	70	180		–	+(9)	+(4)	none	DOD(12)	IORT only
30	B	12	F	DF	conventional, osteoblastic	X-rays bilateral	60	180		–	+(32)	+(10)	none	DOD(33)	IORT only
31	B	12	M	DF	conventional, fibroblastic	X-rays bilateral	70	245	160	+(9)	–	–	EP(11)	DOOC(43)	endoprosthesis
32	B	16	M	DF	conventional, chondroblastic	X-rays bilateral	60	120	90	–	–	+(23)	EP(10)	NED(43)	endoprosthesis
33	B	14	M	PH	conventional, osteoblastic	X-rays AP	60	180		–	–	–	PN(4)	CDF(35)	nailed

results of 33 patients who received IORT between 1978 and 1994 to identify the role of this form of treatment.

Patients and methods

Between 1978 and 1994 IORT was used in the treatment of 36 patients with osteosarcoma. For this retrospective study, our inclusion criteria were : (1) a primary lesion in an extremity; and (2) no evidence of distant matasteses at the beginning of therapy. Thirty-three patients were included in the study (Table 1). There were 24 males and 9 females with a mean age of 15 years (6–53). The primary site of the tumour was the middle or distal thirds of the femur in 20 patients, the proximal tibia in 11 and the proximal humerus in 2. Histological examination of the pre-irradiated tumours revealed that 32 were conventional osteosarcomas and one was a high-grade surface osteosarcoma.

In earlier cases in the series, IORT was used as local adjuvant therapy and subsequent surgical procedures for each case were planned at the beginning of treatment. These patients were categorised as group A. In later cases IORT was regarded as definitive local treatment and irradiated bones were left in situ and no further procedures were performed unless required. These patients were categorised as group B.

Intra-operative radiation therapy

As modifications have been introduced during the 15 years of our experience, current procedures are described here. The tissues to be resected were identified, after preoperative imaging, according to the concept of wide resection described by Enneking [8], and the area to be irradiated was planned to include the entire area to be resected. At operation the lesion to be irradiated was isolated and separated from normal tissue in the axial plane, and the continuity of proximal and distal normal tissue was maintained. After preparation, the area to be irradiated was wrapped in sterile bandages to separate it from the area not being irradiated in the longitudinal plane. In tumours of the femur or tibia irradiation was performed bilaterally. Thus the tissues not being irradiated were retracted posteriorly (Fig. 1). Lesions in the humerus were irradiated anteroposterially while tissues that were to be preserved were retracted medially. Irradiation was administered with electrons of 12–30 MeV or X-rays of 10 MV with a dose of 45–70 Gy. Electrons were delivered by a β-tron (BT-32, Shimadzu Corp., Kyoto), and X-rays were delivered by a linear accelerator (2100, Varian

Fig. 1 IORT for a tumor in the distal femur. Tissues to be irradiated are exposed and wrapped with sterile bandages. Other tissues are retracted away from the field dorsally. Irradiation is given by opposed bilateral directions

Associates, Palo Alto, CA). Among the earlier cases in this series four patients (1–4) received anteroposterior irradiation and another four (5–8) were given combined anteroposterior and bilateral irradiation for a lesion in the distal femur or proximal tibia. Informed consent was obtained from all patients or their guardians.

Chemotherapy

Preoperative chemotherapy was administered in 32 patients; intraarterially in 18 cases, intravenously in 5 cases and by both routes in 9 cases. Postoperative systemic chemotherapy was administered in 32 cases. The chemotherapeutic regimes have changed during the period of this study but most consisted of adriamycin, methotorexate and cisplatinum.

Survival analysis

Survival rates were estimated by the method of Kaplan-Maier [12]. For disease-free survival rate, the end point was defined as the first detection of local recurrence or metastases.

Functional evaluation

Functional evaluation was performed for patients who were able to be followed for at least 12 months and who retained the affected limb at final follow-up. Twenty-two patients in this study met these criteria and were evaluated with the revised 30-point scale of the Musculoskeletal Tumour Society described by Enneking [9]. We excluded the "emotional acceptance" from the evaluation and thus removed 5 points, because no information was available from deceased patients treated early in this series; thus there was a 25-point scale.

Results

There were 7 local recurrences, 2 in group A and 5 in group B (Table 1). All but one of the recurrences were in soft tissue which was retracted from the field of irradiation.

Distant metastases were detected in 21 patients. The median interval from the initiation of treatment to the appearance of metastases was 7 months (2–120) (Table 1).

Sixteen patients died of the disease. The median time from the beginning of treatment to death was 20 months (7–51). Eleven patients remained disease-free at the last evaluation; with a median follow-up of 114 months (35–222).

The final oncological results for each group were: in group A, nine patients died of the disease; in two patients there was no evidence of disease and one patient was continuously disease-free. In group B seven patients died of the disease, one patient died of an unrelated cause, two patients were alive with disease, in one patient there was no evidence of disease and ten patients were continuously disease-free. The disease-free survival rate was 39% at 7 years and 35% at 10 years.

In group A, seven patients underwent prosthetic replacement and two underwent amputation, one as a primary treatment before IORT and one due to extensive postoperative skin necrosis. Five patients underwent amputation for local recurrence, or for the development of a

Table 2 Functional evaluation (femur and tibia). *M* male, *F*, female, *DF* distal femur, *MF* midshaft femur, *PT* proximal tibia

No.	Age	Sex	Site	Pain	Function	Supports	Walking ability	Gait	Total	% Rating	Local status at evaluation (mo.)
1	13	F	DF	5	3	1	3	3	15	60	Endoprosthesis (222)
3	15	M	PT	3	3	1	3	3	13	52	Endoprosthesis (17)
4	17	M	DF	5	1	4	3	1	14	56	Endoprosthesis (12)
5	15	M	DF	5	2	5	3	2	17	68	Endoprosthesis (12)
6	20	M	DF	4	3	6	4	4	20	80	Endoprosthesis (191)
9	11	M	DF	3	1	0	2	1	7	28	IORT only, fractured (12)
11	12	F	DF	3	1	0	2	1	7	28	IORT only, no fracture (12)
13	12	F	PT	5	3	4	4	3	19	76	Endoprosthesis (147)
15	15	M	PT	5	3	3	4	3	18	72	IORT only, no fracture (12)
16	12	F	PT	5	2	3	4	3	17	68	IORT only, no fracture (19)
20	15	M	PT	5	3	3	3	3	17	68	Endoprosthesis (110)
23	20	M	DF	4	3	5	3	3	18	72	Endoprosthesis (12)
24	17	M	DF, MF	5	3	5	4	4	21	84	Nailed, no fracture (13)[a]
25	25	F	DF, MF	5	3	3	4	3	18	72	Nailed, no fracture (18)
26	11	M	DF	5	1	1	2	1	10	40	IORT only, fractured (13)
27	16	M	PT	5	4	5	4	4	22	88	Endoprosthesis (75)
28	17	M	DF	3	3	5	4	3	18	72	Endoprosthesis (70)
30	12	F	DF	4	3	1	3	2	13	52	IORT only, no fracture (12)
31	12	M	DF	5	3	5	5	3	21	84	Endoprosthesis (31)
32	16	M	DF	5	3	5	4	3	20	80	Endoprosthesis (43)

[a] Evaluation before detection and treatment of a skip lesion

Table 3 Functional evaluation (humerus). *M* male, *F* female, *PH* proximal humerus

No.	Age	Sex	Site	Pain	Function	Hand positioning	Dexterity	Lifting ability	Total	% Rating	Local status at evaluation (mo.)
17	12	M	PH	5	1	1	3	2	12	48	IORT only, fractured (122)
33	14	M	PH	5	3	5	5	4	22	88	Nailed, no fracture (35)

pseudarthrosis. Prosthetic replacement was performed in seven patients. Three patients underwent internal stabilisation of the irradiated bone by intramedullary nailing.

Fourteen patients underwent prosthetic replacement of the knee joint. The final status was thus : prosthetic replacement in 13, amputation in 8, internal stabilisation in 3 and no additional surgery in 9 (Table 1).

Twenty-two patients were available for functional analysis, of whom 12 had undergone prosthetic replacement, no additional operations had been performed in 7 and internal stabilisation had been performed in 3. The average functional rating of the patients with prosthetic replacement was 71% (52–88). The average rating for those with internal stabilisation was 81% (72–88), and the average rating for those without further surgery was 48% (8–72). The poor rating for the last group was due to the development of a pseudoarthrosis in three cases and the use of braces or non-weight bearing to prevent fractures in four cases (Tables 2, 3).

Complications

There were significant complications in 26 patients. Fracture of the irradiated bone occurred in 13 patients. Deep infection developed in 4 patients, after surgery secondary to initial IORT.

Seventeen patients suffered skin complications after IORT, 4 in patients with a tumour of the femur, 11 patients with a tumour in the tibia and 2 patients with a tumour in the humerus. The complications were mild and the skin healed satisfactorily, except in two cases, one required a rotation flap, and one underwent amputation.

Nerve damage occurred in 12 patients, 5 in patients with a tumour of the femur, and 7 with a tumour of the tibia. In the two humeral cases, the major nerves were divided to obtain a wide surgical. Partial peroneal palsy due to irradiation was seen in two cases.

Discussion

Prosthetic replacement and allografts are the two main procedures used to restore function after resection of osteosarcomas in extremities. Several problems with prostheses, however, have still to be resolved; such as mechanical failure, loosening at the bone prosthesis interface, and stress shielding. Allografts also present several problems, such as a high infection rate, transmission of viral disease, and inadequate mechanical properties for joint function [4, 25].

Some promising results have been reported with reimplantation. Autoclaved bone has been shown to unite to host bone. Articular cartilage, however, is very vulnerable to heat treatment, and the use of autoclaved bone, including joint surfaces is usually combined with prosthetic replacement [3, 11].

Osteogenesis is preserved after treatment with alcohol, but cartilage degeneration occurs as early as 12 weeks after treatment in the experimental model [19]. Although the rate of bone union at the host-graft junction seemed satisfactory after high-dose extracorporeal irradiation and reimplantation [24], patients were required to remain non weight-bearing for a longer period (12 months) until union was achieved, and the rate of bone necrosis was higher than that seen with other methods. Our method has advantages when compared with the implantation. There is no risk of pseudoarthrosis at the host graft junction. Articular cartilage was maintained [20]. Structures necessary for joint stability are divided in methods such as autoclaving or extracorporeal irradiation, causing gross instability. One of the disadvantages of IORT is that the exposure of the irradiated field requires extensive local dissection, which can cause vascular insufficiency. The local complication rate in this series is higher than those in the literature for other limb-saving treatments (36–71%) [3, 4, 7, 10, 22]. The major complication, threatening the outcome, is a fracture of the irradiated bone. The strength of bone decreases after irradiation [18] as does vascularity, and there is an increase in local osteoporosis [21]. The most significant factor for oncological control of osteosarcoma is the width of the margin of excision at operation; and the critical aspect of IORT is determining the plane between irradiated and non-irradiated tissues. Histological examination of the resected tissue after IORT shows necrosis of the tumour [13, 16]. The local recurrence rate in this series was higher than that in the literature (5–14%) [6, 7, 10, 11, 22], suggesting inappropriate determining of the margin in some cases. The oncological and functional results in this group of patients is not satisfactory. During pre-operative planning in each case, the advantages of IORT must be weighed against the anticipated extent of tissue dissection required to achieve a wide enough margin while retracting normal tissues away from the field of irradiation. In order to obtain a functional limb in the long-term after IORT, critical patient selection and improvements in the protocol and technique are required. Since 1995 we have used a higher dose of radiation and preventative intramedullary nailing is used routinely, sometimes in combination with bone cement; and the final evaluation of the place of IORT in the treatment of osteosarcoma remains to be identified.

References

1. Abe M, Takahashi M, Yabumoto E, Adachi H, Yoshii M, Mori K (1980) Clinical experiences with inteaoperative radiotherapy of locally advanced cancers. Cancer 45:40–48
2. Alman BA, De-Bari A, Krajbich JI (1995) Massive allografts in the treatment of osteosarcoma and Ewing sarcoma in children and adolescents. J Bone Joint Surg Am 77-A:54–64
3. Asada N, Tsuchiya H, Kitaoka K, Mori Y, Tomita K (1997) Massive autoclaved allografts and autografts for limb salvage surgery. A 1–8 year follow-up of 23 patients. Acta Orthop Scand 68:392–395
4. Brien EW, Terek RM, Healey JH, Lane JM (1994) Allograft reconstruction after proximal tibial resection for bone tumors. An analysis of function and outcome comparing allograft and prosthetic reconstructions. Clin Orthop 303:116–127

5. Capanna R, Morris HG, Campanacci D, Del Ben M, Campanacci M (1994) Modular uncemented prosthetic reconstruction after resection of tumours of the distal femur. J Bone Joint Surg Br 76-B:178–186
6. Cara JA, Canadell J (1994) Limb salvage for malignant bone tumors in young children. J Pediatr Orthop 14:112–118
7. Eckardt JJ, Eilber FR, Rosen G, Mirra JM, Dorey FJ, Ward WG, Kabo JM (1991) Endoprosthetic replacement for stage IIB osteosarcoma. Clin Orthop 270:202–213
8. Enneking WF, Spanier SS, Goodman MA (1980) A system for the surgical staging of musculoskeletal sarcomas. Clin Orthop 153:106–120
9. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ (1993) A system for the functional evaluation of reconstructive procedures after surgical treatment of tumours of the musculoskeletal system. Clin Orthop 286:241–246
10. Gebhardt MC, Flugstad DI, Springfield DS, Mankin HJ (1991) The use of bone allografts for limb salvage in high-grade extremity osteosarcoma. Clin Orthop 270:181–196
11. Harrington KD, Johnston JO, Kaufer HN, Luck JV Jr, Moore TM (1991) Limb salvage and prosthetic joint reconstruction for low-grade and selected high-grade sarcomas of bone after wide resection and replacement by autoclaved autogeneic grafts. Clin Orthop 211:180–214
12. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observation. J Am Statist Assn 53:457–481
13. Kotoura Y, Yamamuro T, Kasahara K (1991) Histological studies of the effect of intra-operative radiation therapy. In: Abe M, Takahashi M (eds) Intra-operative Radiation Therapy. Pergamon Press, New York, pp 373–375
14. Kropej D, Schiller C, Ritschl P, Salzer-Kuntschik M, and Kotz R (1985) The management of IIB osteosarcoma. Experience from 1976 to 1985. Clin Orthop 270:40–44
15. Malawer MM, Chou LB (1995) Prosthetic survival and clinical results with use of large-segment replacements in the treatment of high-grade bone sarcomas. J Bone Joint Surg Am 77-A:1154–1165
16. Nagashima T, Yamamuro T, Kotoura Y, Takahashi M, Abe M, Nakashima Y (1983) Histological studies on the effect of intra-operative irradiation for osteosarcoma. J Jpn Orthop Assoc 57:1681–1697
17. Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ (1994) Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. A long-term oncological, functional, and quality-of-life study. J Bone Joint Surg Am 76-A:649–656
18. Sugimoto M, Takahashi S, Toguchida J, Kotoura Y, Shibamoto Y, Yamamuro T (1991) Changes in bone after high-dose irradiation. Biomechanics and histomorphology. J Bone Joint Surg Br 73-B:492–497
19. Sung HW, Wang HM, Kuo DP, Hsu WP, Tsai YB (1986) EAR method: An alternative method of bone grafting following bone tumor resection (a preliminary report). Semin Surg Oncol 2:90–98
20. Takahashi S, Sugimoto M, Kotoura Y, Oka M, Sasai K, Abe M, Yamamuro T (1992) Long-lasting tolerance of articular cartilage after experimental intraoperative radiation in rabbits. Clin Orthop 275:300–305
21. Takahashi S, Sugimoto M, Kotoura Y, Sasai K, Oka M, Abe M, Yamamuro T (1994) Long-term changes in the haversian systems following high-dose irradiation. J Bone Joint Surg Am 76-A:722–738
22. Tsuchiya H, Tomita K (1992) Prognosis of osteosarcoma treated by limb-salvage surgery: the ten-year intergroup study in Japan. Jpn J Clin Oncol 22:347–353
23. Unwin PS, Cannon SR, Grimer RJ, Kemp HBS, Sneath RS, Walker, PS (1996) Aseptic loosening in cemented custom-made prosthetic replacements for bone tumours of the lower limb. J Bone Joint Surg Br 78-B:5–13
24. Uyttendaele D, De Schryver A, Claessens H, Roels H, Berkvens P, Mondelaers W (1988) Limb conservation in primary bone tumours by resection, extracorporeal irradiation and re-implantation. J Bone Joint Surg Br 70-B:348–353
25. Wilkins RM (1998) Complications of allograft reconstructions. In: Simon MA, Springfield D (eds) Surgery for Bone and Soft-tissue Tumors. Lippincott-Raven Publishers, Philadelphia, pp 487–496
26. Yamamuro T, Kotoura Y, Kasahara K, Iwasaki R, Takahashi M, Abe M (1991) Limb salvage with the intraoperatively irradiated tumor tissues preserved in situ in osteosarcoma. In: Langlais F, Tomeno B (eds) Limb Salvage-Major Reconstructions in Oncologic and Nontumoral Conditions. Springer, Berlin Heidelberg New York pp 619–625
27. Zwart HJJ, Taminiau AHM, Schimmel JW, van Horn JR (1994) Kotz modular femur and tibia replacement. 28 tumor cases followed for 3 (1–8) years. Acta Orthop Scand 65: 315–318