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Advances in bone tumour treatment in 30 years with respect to survival and limb salvage. A single institution experience

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Abstract We analysed 721 patients with primary malignant bone tumours treated in a single institution with regard to diagnosis, treatment and prognosis. From 1965 to 1974, 154 patients were treated, of whom 17% had no surgery, 36% underwent resection and 46% underwent amputation. Margins of resection were intralesional in 21%, 72% of patients received chemotherapy and overall survival rate was 24%. From 1975 to 1984, 174 patients were treated, of whom 12% had no surgery, 54% underwent limb salvage procedures and 34% underwent amputation or resection-replantation. Margins of resection were intralesional in 16% 67% of patients received chemotherapy and overall survival rate was 46%. From 1985 to 1994, 393 patients were treated, of whom 7% had no surgery, 77% underwent limb salvage procedures – mainly with endoprostheses – and 15% underwent amputation or resection-replantation. Margins of resection were intralesional in 12%, 68% of patients received chemotherapy and overall survival rate was 62%. Advancements in the treatment of primary malignant bone tumours justify limb salvage procedures in combination with highly effective polychemotherapy in specialised centres and has resulted in an overall survival rate of more than 60%.

Résumé 721 malades porteur d'une tumeur osseuse maligne primitive traités dans une seule institution ont été analysés quant à diagnostic, traitement et pronostic. De 1965 à 1974, parmi 154 malades traités, 17% n'avaient aucune chirurgie, 36% ont eu une résection et 46% ont subi l'amputation. Les marges de résection étaient intralésionelles dans 21% des cas. 72% des malades ont reçu de la chimiothérapie. La survie totale était de 24%. De 1975 à 1984, parmi 174 malades traités, 12% n'avaient aucune chirurgie, 54% ont subi des procédures du sauvetage du membre et une amputation ou résection – replantation était exécuté dans 34%. Les marges de résection étaient intralésionelles dans 16% des cas. 67% des malades ont reçu de la chimiothérapie. La survie totale était 46%. De 1985–1994 393 malades ont été traités de que 7% n'avaient aucune chirurgie, 77% ont subi des procédures du sauvetage du membre avec endoprosthèses et amputation ou résection – replantation a été exécuté dans 15%. Les marges de résection étaient intralesionales dans 12%. 68% des malades ont reçu la chimiothérapie. La survie totale était 62%. Les avancements dans le traitement de tumeurs osseuses malin primaires justifient des procédures du sauvetage du membre dans combinaison avec polychimiothérapie très efficace dans les centres spécialisés et ont résulté en un taux de la survie total de plus que 60%.

This study was conducted in conjunction with the Vienna Registry for Bone and Soft Tissue Tumors (Head: Prof. Dr. M. Dominkus), founded in 1964 as the Vienna Bone Tumor Registry

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Introduction

Between January 1, 1965 and December 31, 1994, 1,716 patients with primary tumours and tumour-like lesions of the bone were registered in the Vienna Registry for Bone and Soft Tissue Tumors [17]. Of these patients, 721 had a primary malignant bone tumour. All registered patients, including those who had received no treatment due to either late referral, refusal to undergo therapy or death under treatment were included in the study.

The tumour registry continuously monitors and follows the patients. When a patient does not appear for their regular annual appointment the Bureau of Vital

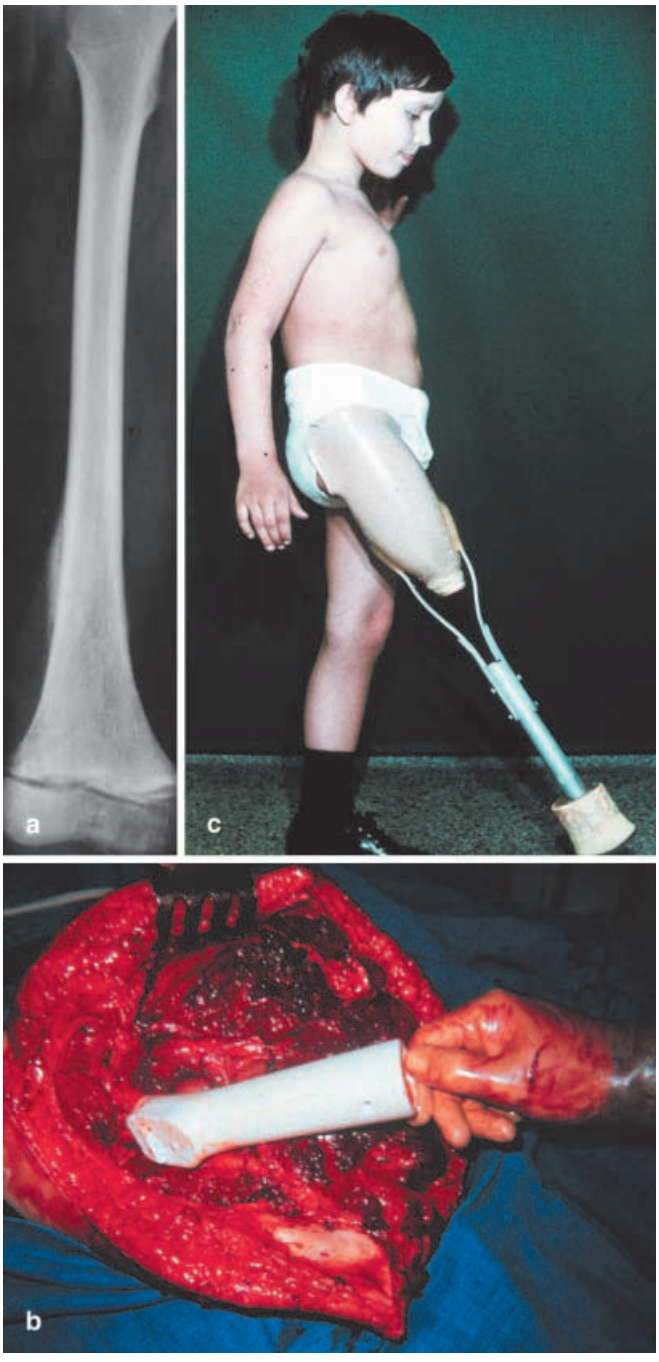

Fig. 1 A 9-year-old boy with osteosarcoma in the right distal femur. Hip disarticulation May 1974. **a** X-ray (anteroposterior view), **b** hip disarticulation followed by implantation of a ceramic hemiprosthesis to provide support for a femoral orthosis, **c** patient wearing the orthosis († September 1974)

Statistics in Austria is contacted. If the patient has died, the date of death is reported. This procedure makes it possible to give conclusive statements on prognosis and treatment of different tumour types. In keeping with highly malignant tumours the prognostic risk period for bone tumours is 3 years. We therefore consider we are justified in making prognostic statements on patients treated at our institution with a minimum of 3 years follow-up.

Patients and methods

In order to compare various treatment modalities as to prognosis and survival, we subdivided the whole period into three sections: (1) Period 1 (January 1965–December 1974), i.e. prior to the introduction of effective multidrug regimens. Surgical treatment mainly consisted of amputation (Fig. 1a–c). (2) Period 2 (January 1975–December 1984), the period of effective multi-drug chemotherapy [6, 8, 14, 15, 16, 25]. Surgical treatment consisted of amputation and resection-replantation [11, 23] (Fig. 2a–d) and limb salvaging procedures in selected cases combined with implantation of endoprostheses [9]. (3) Period 3 (January 1984–December 1994), the period marked by the application of highly effective chemotherapy protocols [7, 24]. Surgical treatment was mainly resection of the tumour and reconstruction using endoprostheses [10] (Fig. 3a–d).

The histological diagnoses were similarly distributed within the three periods, with 45–50% osteosarcoma, 15–20% Ewing's sarcoma and primitive neuroectodermal tumours (PNET) and 12–17% chondrosarcomas. The comparable numbers of patients receiving chemotherapy in the three periods, independent of the success of treatment, is due to the nearly equal percentage of patients suffering from highly malignant bone tumours.

Radiotherapy was not analysed since, on the one hand, the application of this modality did not change over the years and, on the other hand, radiation therapy was not a major factor influencing the prognosis of primary Ewing's sarcoma of bone [7].

Survival analysis was computed according to Kaplan-Meier, and statistical significances were determined with the log-rank test. If the log-rank test showed a significant difference between the three periods, the latter were compared in pairs in a second step. By this procedure the multiple level α is controlled.

Results

Between January 1965 and December 1974, 72% of the patients (111/154) underwent ineffective chemotherapy – in most cases with single substances. Analysis of surgical treatment revealed a large number of intralesional resections (33=21.4%) and no operations (27=17.5%), amounting to a total of 38.9%. Most patients underwent transmedullary amputation (Table 1). Of 154 patients, only 37 (24%) survived.

Between January 1975 and December 1984, effective chemotherapy protocols [14, 15, 16, 24, 25] were used and the survival rate increased to 46% (80/174); 67.2% of patients (117/174) underwent multidrug chemotherapy (Table 2). The number of limb salvaging procedures (implantation of endoprostheses *n*=46, resections *n*=20)

Table 1 Type of chemotherapy, type of primary surgery and patient survival from 1965–1974 (*n*=154)

Chemotherapy	Polychemotherapy	50	32.5%
	Monochemotherapy	61	39.6%
	No chemotherapy	43	27.9%
Type of primary surgery	Amputation	71	46.1%
	Resection – extralesional	23	15.0%
	Resection – intralesional	33	21.4%
	No surgery	27	17.5%
Survival	Died within 3 years post-surgery	85	55.2%
	Died	117	76.0%
	Alive	37	24.0%

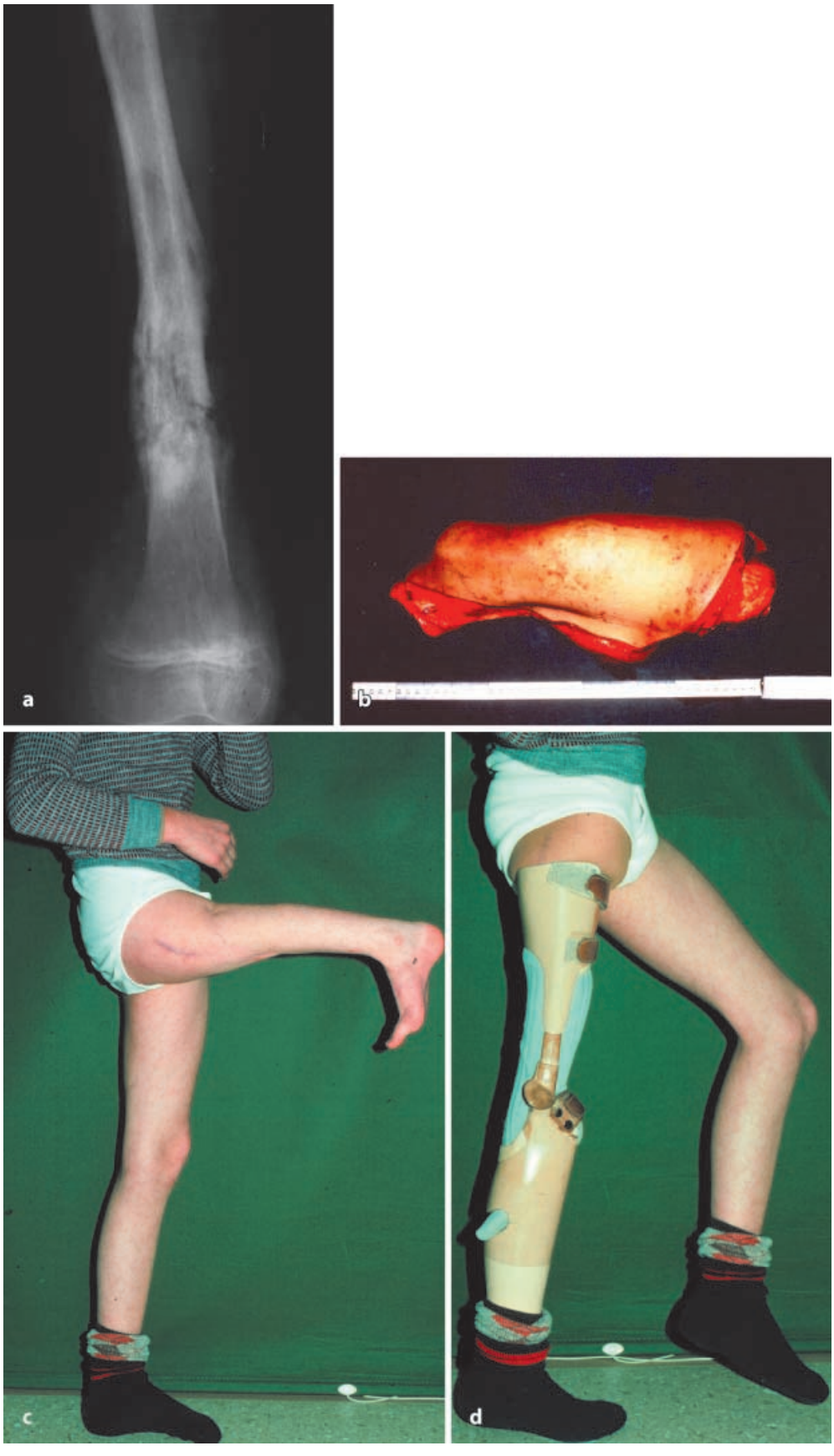

Fig. 2 A 10-year-old boy with osteosarcoma in the right distal femur. Rotationplasty September 1981. **a** X-ray (anteroposterior view), **b** resected distal femur with unopened knee joint, **c** full active flexion in hip and ankle joint, **d** clinical aspect with the orthosis (disease-free survival March 2000)

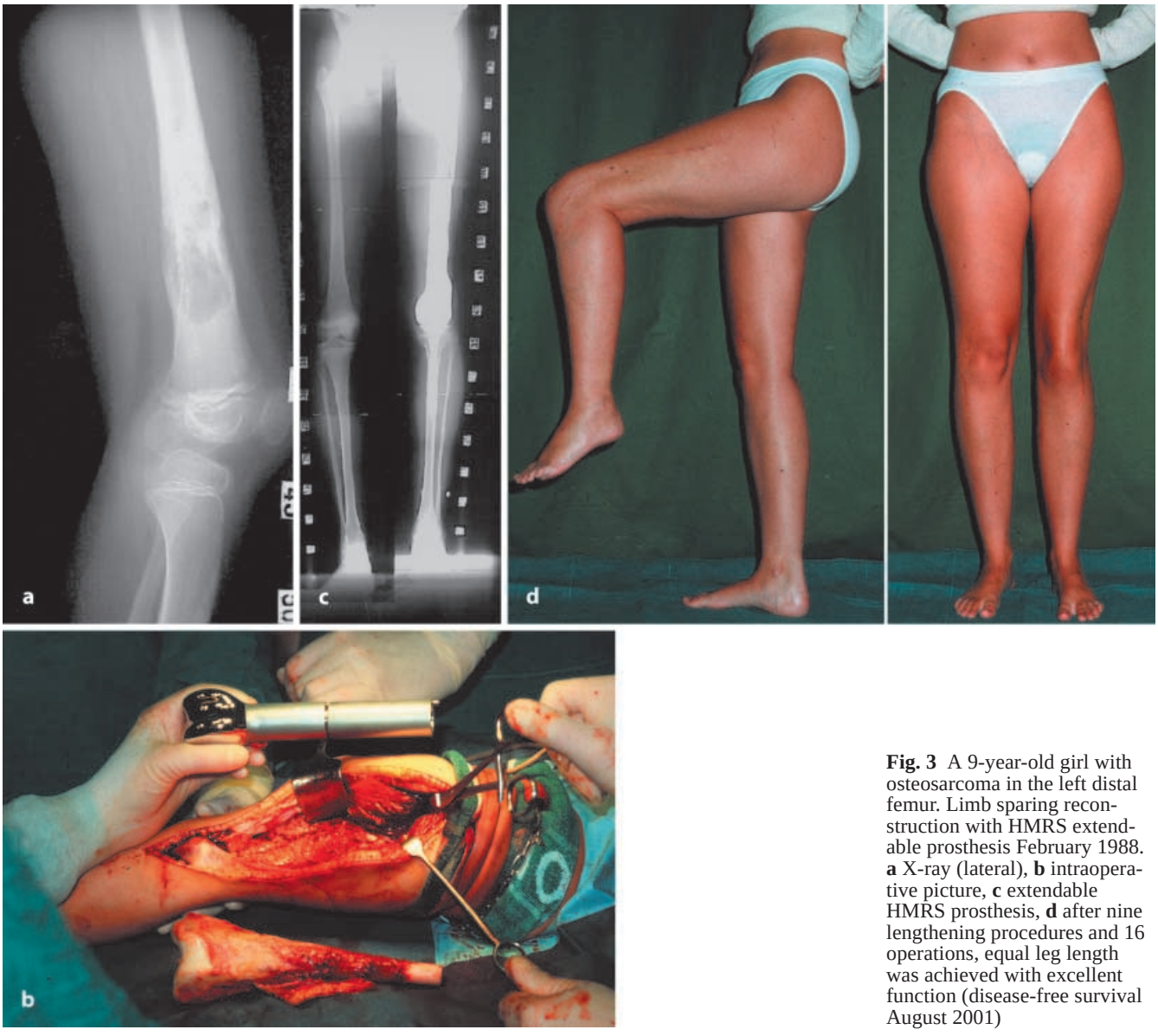

Fig. 3 A 9-year-old girl with osteosarcoma in the left distal femur. Limb sparing reconstruction with HMRS extendable prosthesis February 1988. **a** X-ray (lateral), **b** intraoperative picture, **c** extendable HMRS prosthesis, **d** after nine lengthening procedures and 16 operations, equal leg length was achieved with excellent function (disease-free survival August 2001)

Table 2 Type of chemotherapy, type of primary surgery and patient survival from 1975–1984 (*n*=174)

Chemotherapy	Osteosarcoma protocol	90	51.7%
	Ewing's sarcoma protocol	27	15.5%
	No chemotherapy	57	32.8%
Type of primary surgery	Amputation	35	20.1%
	Rotationplasty	24	13.8%
	Endoprostheses	46	26.4%
	Resection – extralesional	20	11.5%
	Resection – intralesional	28	16.1%
	No surgery	21	12.1%
Survival	Died within 3 years post-surgery	68	39.1%
	Died	94	54.0%
	Alive	80	46.0%

Table 3 Type of chemotherapy, type of primary surgery and patient survival from 1985–1994 (*n*=393)

Chemotherapy	Osteosarcoma protocol	177	45.0%
	Ewing's sarcoma protocol	75	19.1%
	Others	14	3.6%
	No chemotherapy	127	32.3%
Type of primary surgery	Amputation	36	9.2%
	Resection-replantation	24	6.1%
	Resection with endoprosthesis	196	49.8%
	Resection without endoprosthesis	109	27.8%
	No surgery	28	7.1%
Survival	Died within 3 years post-surgery	109	27.7%
	Died	151	38.4%
	Alive	242	61.6%

Table 4 Type of surgery and resection margins in the period 1985–1994

Surgery type	Overall		Amputation	Resection-replantation	Resection with endoprosthesis	Resection without endoprosthesis
Wide or radical margins (Enneking)	286	72.8%	35	24	175	52
Resection – marginal	21	5.4%	1		12	8
Resection – intralesional	50	12.7%			3	47
Resection margins not determined	8	1.0%			6	2
Total surgery	365	92.8%	36	24	196	109
No surgery	28	7.2%				
Total cases	393	100.0%				

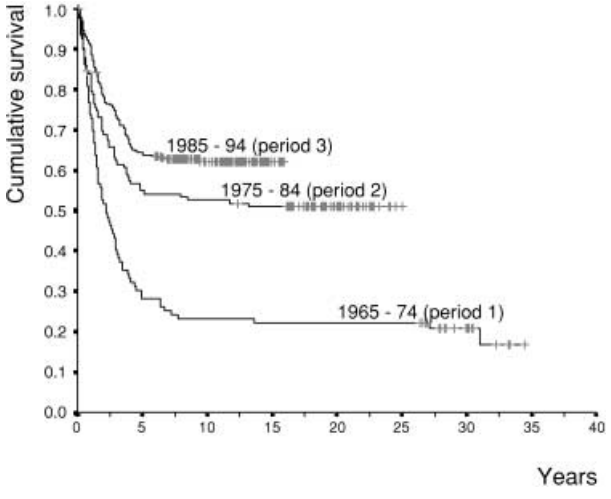

Fig. 4 Overall survival of 485 patients (1965–1974: 100 patients, 1975–1984: 123 patients, 1985–1994: 262 patients) suffering from osteosarcoma, Ewing's sarcoma and PNET. Increase in overall survival between the three periods is statistically significant: Periods 1 and 2, log-rank $P<0.0001$; periods 1 and 3, log-rank $P<0.0001$

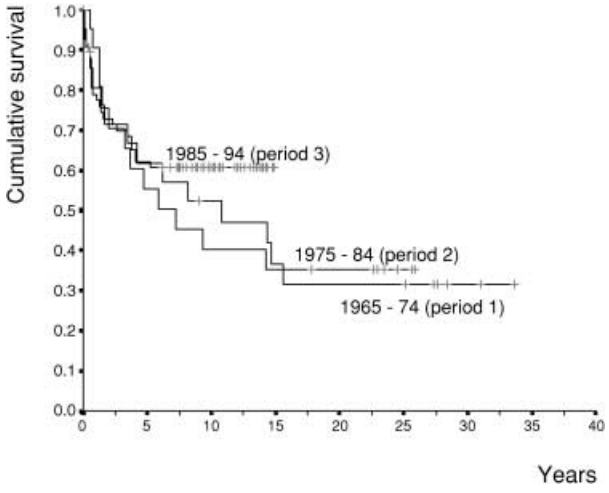

Fig. 5 Overall survival of 110 patients (1965–1974: 22 patients, 1975–1984: 21 patients, 1985–1994: 67 patients) suffering from chondrosarcoma. Increase in overall survival between the three periods is not statistically significant: log-rank $P=0.49$

increased to 38% and equalled the numbers of amputations (n=35) and resection-replantations (n=24); 28 (16.1%) had intralesional resections and 21 (12.1%) had no surgery (total 28.2%). Of 174 patients, 80 (46%) survived.

Between January 1985 and December 1994, primarily, the successful COSS 86 protocol [4] was applied in patients with osteosarcoma, while the CESS 86 and CESS 91 protocols [13] were used in those suffering from Ewing's sarcoma with a satisfactory outcome. Survival rate for osteosarcoma was 72% [4] and for Ewing's sarcoma 60% [7]; 266 patients (67.7%) received chemotherapy while 127 (32.3%) with low-grade tumours (e.g. chondrosarcoma, parosteal osteosarcoma, etc.) did not. Surgical method of choice was resection. Endoprostheses were implanted in 196 patients. Children were provided with extendable prostheses [18] while patients with pelvic tumours were given pelvic prostheses [22]. One hundred nine patients underwent biological reconstruction (Table 3). Percentage of amputations (n=36) and resection-replantations (n=24) [11, 23] was reduced to 15.3%. In most cases intralesional resection margins could be avoided. They were observed mainly in resections without implantation of an endoprosthesis, in tumours of the pelvic region and spine (47/109) (Table 4), and were seen in 50 patients (12.7%). Of 393 patients, 242 (61.6%) survived (Table 3).

The main reason for improvement in the second and third periods – reflected in a significant improvement in survival rate, especially among patients with osteosarcoma [4, 5, 24] and Ewing's sarcoma [7, 13] – was the introduction of effective neo-adjuvant multidrug chemotherapy (Fig. 4). No improvement was achieved in patients who received no chemotherapy, as is reflected by the results for chondrosarcoma (Fig. 5).

Discussion

Our tumour registry shows that the therapeutic strategy used for bone tumours has been changing over the last 3 decades. As a result, the survival rate of patients with primary malignant bone tumours is steadily increasing. The prevailing opinion as to the necessity of chemotherapy in high-grade lesions was not substantially different in the three periods. However, a significantly wider range of effective chemotherapy regimens was available in the second and third periods in contrast

to the first. In the third period, surgical margins were determined according to Enneking [2] in all but eight cases and revealed a high percentage of wide and radical margins, especially in the largest group, which was subjected to resection and replacement with endoprostheses. Resections without endoprosthetic replacement were mainly performed in the spine and pelvic region, as well as in cases with extensive soft-tissue involvement. Only these cases showed less optimal margins. Nevertheless, the overall results, indicating a survival rate of 61.6%, clearly justify the use of this procedure in specialised centres. The critical argument of repeated revisions being required in patients provided with endoprostheses [1] is counterbalanced by the fact that the functional outcome in these patients is good and the quality of life remains high, even after several revisions [3]. One problem during the first two periods was the high rate of intralesional resections within the pelvis and the spinal region when en bloc resection without implantation of a prosthesis was used. This feature has been improved by advancements in surgical technique [12, 22], as reflected by 47 intralesional resections only in the third period. In certain subgroups, such as osteosarcomas in children and adolescents [19] or Ewing's sarcoma [20, 21], results were considerably better than the overall outcome. A truly comparable parameter for progress in bone tumour therapy is death within 3 years. Death within 3 years was reduced to 55.2% in the first period, to 39.1% in the second and, finally, to 27.7% in the third, which were significant differences (Tables 1, 2) and 3.

In the treatment of malignant bone tumours the turning point in terms of better survival was achieved in 1975 when effective multidrug chemotherapy was introduced. A further turning point with regard to limb salvage and maintenance of body integrity was the introduction of technically improved endoprostheses in 1985. Although these results justify the transition from amputation to limb salvaging procedures at our institution, amputation may still be a life-saving and indispensable measure.

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