Surgical outcomes in osteosarcoma

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From the European Osteosarcoma Intergroup study 202 patients were assessed with respect to their surgical treatment. Although treated in three different centres the survival of the three groups was identical (57% at five years). Two of the centres had rates of limb salvage of 85% and 83%, respectively, while the third had a rate of 49%. The corresponding risks of local recurrence were 13.3%, 6.8% and 2.5%, with all local recurrences arising in limbs with attempted limb salvage. Local recurrence was closely related to the adequacy of the margins of excision and to the chemotherapeutic response. Patients who had undergone limb-salvage surgery and who developed local recurrence still had a better survival than those who had primary amputation (37% v 31% survival at five years). Of patients who relapsed, 31% of those with local recurrence alone were cured by further treatment, as compared with only 10% of those with metastases. Limb-salvage surgery with effective chemotherapy remains the optimum treatment for osteosarcoma.

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Osteosarcoma remains a challenging condition to treat. Despite the advances in surgery and chemotherapy over the past 25 years there remains a cohort of patients who do not survive. Numerous studies have been carried out in an attempt to improve the overall rate of survival for this condition. Despite this, rates of cure have remained unchanged at around 55% to 70% for the past 15 years.¹⁻⁴

During this period limb salvage surgery has become more commonly practised, and in many centres will now be offered to 80% or more of patients presenting with osteosarcoma. Simon et al⁵ and Rougraff et al⁶ have shown that the survival of patients with either limb salvage or amputation is no different, even though there is a higher rate of local recurrence in patients with limb salvage. It is generally accepted that, provided the surgery is carried out in an appropriate oncological manner, there is no detriment to the survival of patients treated with limb salvage in a variety of techniques.

The European Osteosarcoma Intergroup (EOI) has now completed two studies on osteosarcoma. In the first, which took place between 1983 and 1986, 198 eligible and assessable patients were randomised to receive either a two-drug regime of doxorubicin and cisplatin or a three-drug regime of doxorubicin, cisplatin and high-dosage methotrexate.⁷ The overall survival was 57% and the two-drug regime was found to be superior, in terms of disease-free survival, to the three-drug regime.

The second EOI study ran from 1986 to 1993. A total of 391 eligible patients with non-metastatic peripheral osteosarcoma were entered into the study in order to compare the previous two-drug regime with a multidrug regime based on the T10 protocol.⁸ The results showed no significant difference between the two regimes, with an overall survival of 55% at five years. In that study, 101 of 391 patients (26%) had an amputation, seven had a rotationplasty and the remainder had limb-salvage surgery.

We now present a more detailed analysis of the surgical aspects of this study based on the experience of the three leading contributory centres. It is an attempt to identify the aspects of treatment which contributed to the outcome, both in terms of survival and local control.

Patients and Methods

Patients under the age of 40 years with peripheral non-metastatic high-grade osteosarcoma were eligible for inclusion in the trial. Those with low-grade osteosarcoma and osteosarcoma of the pelvis and axial skeleton were excluded. Patients were randomised to receive one of the two arms of chemotherapy. Surgical and other treatment decisions were determined locally. The original study was a trial of chemotherapy and few surgical data were collected.

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Since 61 centres contributed patients to the original study, it proved to be impracticable to obtain accurate information from all the treating centres with regard to surgical methods and outcomes. Three centres were found to have contributed 202 of the patients (52%) and it was decided to use information from these centres for a more detailed analysis of the surgical outcome.

Data for the 202 patients were checked and verified by the surgeons from the treating centres. Considerably more data than had been required for the original trial were collected for analysis, including details about the size of the tumour, volume, level of alkaline phosphatase at diagnosis, surgical factors and outcome as well as complications. Follow-up data were obtained in 1998 allowing a median follow-up of 110 months (72 to 144). The three centres, designated A, B and C, treated 39, 60 and 103 patients, respectively.

Operative treatment. One centre (A) had a preference for allograft replacements and rotationplasty while the other two used endoprosthetic replacements for limb salvage. Rotationplasty was usually used in patients when the only alternative would have been an amputation and therefore, for this particular analysis, they have been regarded as amputations. The margins of excision were assessed using the standard terms devised by Enneking, Spanier and Goodman.⁹ Excisions which were wide or radical were judged to be adequate while intralesional or marginal excisions were labelled marginal.

Statistical analysis. Differences between groups were assessed using the chi-squared test. Overall survival was calculated using Kaplan-Meier survival curves and the impact of prognostic factors was assessed using the log-rank test.^{10,11} Significance was set at $p < 0.05$. When investigating the significance of tumour and patient characteristics, the survival time was calculated from the time of diagnosis. When surgical factors and factors linked to local recurrence were analysed, the survival from the date of surgery was used. Confidence intervals (CI) were calculated as appropriate.

Results

Details of the patients. There were 202 patients with a ratio of men to women of 1.9:1. The median age was 17 years (5 to 40). The median length of the tumour was 11 cm (2 to 30) and the median volume was 271 ml (4 to 3386). The most common site of the tumour was the distal femur (105) followed by the proximal tibia (51), proximal humerus (21), fibula (13), and proximal femur (6). Only 13 patients presented with pathological fractures.

Planned and actual treatment. In the original trial the surgeon was required to state the planned surgery at the time of randomisation. This could then be modified by the time of the definitive surgery which usually took place between seven and nine weeks after chemotherapy had begun.

Of 194 patients for whom a preoperative surgical plan

had been made, 142 who had been planned to have limb-salvage surgery subsequently received it, and 22 who had been planned to have an amputation also underwent it. There were 22 patients who had been planned to have limb-salvage surgery, but who underwent amputation. Eight patients planned for amputation had limb salvage.

In the total group, there were 40 amputations and eight rotationplasties. A total of 154 patients had limb-salvage surgery; 126 endoprosthetic replacements, 13 allografts and 15 simple excisions of expendable bones without reconstruction (e.g., fibula, metatarsal).

The size and volume of the tumour varied between those having amputations and those having limb salvage. The median length of tumour requiring amputation was 13.0 cm and 10.8 cm for limb salvage (Mann-Whitney U test, $p = 0.01$). The differences in volume were more obvious. Amputated limbs had a median tumour volume of 374 ml and limb-salvage tumours 235 ml (Mann-Whitney U test, $p = 0.001$).

The median duration of surgery was 2.0 hours for amputations, 3.2 hours for limb salvage and 7.2 hours for rotationplasty. Allografts took a mean of six hours. The median time until chemotherapy was restarted after surgery was 18 days for amputees, 17 for limb-salvage patients and 27 for those with rotationplasty. This also varied between centres. Centre C recommended chemotherapy at 15 days after surgery, centre B after 21 days and centre A after 26 days.

Margins. The margins of excision were judged to be adequate in all but one of the 40 amputations and all of the eight rotationplasties. Of the 154 limb-salvage procedures, 38 (25%) were found to have marginal margins. The incidence of marginal margins was greatest after limb-salvage surgery of fibular tumours (4 of 11).

Response to chemotherapy. Of the 175 patients in whom necrosis was estimated, 28 (16%) had necrosis of over 90%. All but one of those who responded well to chemotherapy had limb-salvage surgery. By contrast, 80% of the patients who received limb-salvage surgery, 97% of those who underwent amputation and all who received a rotationplasty had a poor response with less than 90% necrosis. All those having an unplanned amputation had a poor response. The surgeon was asked to assess clinically the response to chemotherapy; 71% were thought to have responded and 29% of the tumours seemed to increase in size despite chemotherapy. These clinical impressions were linked closely to the percentage necrosis as assessed at histological examination (chi-squared test 5.19, $p < 0.05$).

Differences between the centres. The characteristics of the three groups of patients were broadly similar in terms of age, gender, location of tumour, size of tumour, level of alkaline phosphatase, etc (Table I). Centre A treated fewer children than the other two centres and had a higher median age of patient. There was, however, a marked difference in the surgical management of the patients. More than half of the patients at centre A underwent amputation or rotationplasty, compared with 15% and 17% at the other two centres. No clear reason could be identified for this and it

Table I. Details of the patients and tumours treated at the three centres

	Centre A	Centre B	Centre C	Total
Total number treated	39	60	103	202
Male:female	26:13	44:16	63:40	133:69
Median age (years)	23	16	16	17
Ratio of raised to normal alkaline phosphatase levels (n = 193)	31:7	23:37	63:32	117:76
Median length of tumour (cm)	10	12	10	11
Median volume of tumour (ml)	262	334	158	271
Ratio of proximal to distal tumours	4:35	11:49	13:90	28:174
Proportion with >90% necrosis (%)	17	16	16	16
Pathological fracture	4/39	4/60	5/103	13/202
Proportion having limb salvage (%)	44	85	83	76
Proportion having amputation or rotationplasty (%)	56	15	17	24
Proportion with adequate margins (%)	95	77	77	80
Five-year overall survival (%)	54	59	56	57
Local recurrence rate (%)	2.5	13.5	6.8	8.0

Table II. Details of the presenting and treatment factors which were significant for overall survival on univariate analysis. A high hazard ratio implies an increased risk to overall survival in the presence of that factor. A lower hazard ratio (<1) implies a risk less than unity

	Number at risk (degree of freedom)	Hazard ratio	95% CI	p value
Presenting				
Male:female	133:69 (1)	1.0	0.65 to 1.75	0.44
Age (less than 16 years)	75:127 (1)	1.0	0.98 to 1.04	0.9
Length of tumour >10 cm ³	115:60 (1)	1.6	1.0 to 2.7	0.04
Volume of tumour >100 ml ³	105:25 (1)	2.2	1.02 to 4.95	0.04
Volume of tumour >150 ml ³	94:35 (1)	2.02	1.05 to 3.9	0.03
Pathological fracture	13:166 (1)	1.8	0.78 to 4.1	0.16
Normal alkaline phosphatase level	76:118 (1)	0.43	0.26 to 0.71	0.0009
Distal tumours (not proximal humerus or proximal femur)	174:28 (1)	0.451	0.265 to 0.77	0.003
Treatment centre A:B:C	39:60:103 (2)			0.78
Treatment				
Clinical response to chemotherapy	51:151 (1)	0.32	0.20 to 0.50	p<0.0001
Altered plan from limb salvage to amputation	22:172 (1)	2.4	0.79 to 7.4	0.12
Amputation as opposed to limb salvage	48:154 (1)	3.0	1.9 to 4.7	p<0.0001
Margins of resection, marginal	39:159 (1)	1.5	0.9 to 2.4	0.1
Less than 90% necrosis	28:147 (1)	3.57	1.4 to 8.8	0.006
Local recurrence	16:186 (1)	1.7	0.9 to 3.2	0.09

was felt that patients at centres B and C were more likely to be offered limb-salvage surgery in situations where an amputation or rotationplasty would be carried out at centre A. This was confirmed by the figures for the adequacy of surgical resection which showed that centre A achieved 95% adequate margins compared with 77% at both of the other centres. The proportion of patients at each centre with a good response to chemotherapy was identical. The duration of surgery was not related to the outcome in terms of either survival, early postoperative complications or local recurrence.

Overall survival. The overall survival of these patients was 57% (95% CI 54 to 60) at five years (Fig. 1) and 54% (95% CI 50 to 57) at ten years. There was no difference in survival between the three centres, despite the differences in surgical philosophy (Table I). Univariate analysis showed that a raised alkaline phosphatase, tumours of the proximal femur or distal humerus, and a poor response to chemotherapy were the three most significant prognostic factors to indicate a poor outcome (Table II). Amputation as opposed to limb salvage appeared to be a significant risk

factor on univariate analysis (Fig. 1). This significance was lost on multivariate testing although location of the tumour and a raised level of alkaline phosphatase at diagnosis remained the two most significant factors, as well as the response to chemotherapy.

Local control. The overall incidence of local recurrence (LR) was 8%, but this masked a wide variation both by centre and by type of surgery. The incidence of LR at the three centres was 2.5% (centre A), 13.3% (centre B), and 6.8% (centre C). There were no LRs in patients who had amputation, allograft, simple excision or rotationplasty. All of the LRs arose in those who had undergone limb-salvage surgery with endoprosthetic replacement. The overall incidence was 13.7% in this group. Ten of the 68 patients who received a distal femoral replacement subsequently developed LR (14.7%) which was a similar proportion to that seen in the upper tibia (4 of 33, 12%). Two of the 11 proximal humeral replacements developed LR. It was not seen after proximal femoral replacement.

In this series, no patient with a response to chemotherapy which showed over 90% necrosis developed LR. In this

Fig. 1

Kaplan-Meier curve showing the overall survival after surgery.

Fig. 2

Kaplan-Meier curve showing the risk of developing a local recurrence.

Fig. 3

Kaplan-Meier survival curves for patients with tumours with poor prognosis.

limb-salvage group LR was associated with the size of the tumour (>500 ml $p = 0.003$) and the margin of excision (>0.0001) (Fig. 2). Four of the six patients with large (>500 ml) tumours, marginal surgical margins and a poor response to chemotherapy developed LR. No patient with over 90% necrosis developed LR, even if the excision was marginal, but 36% of patients with a marginal excision and a poor response to chemotherapy developed LR. There was a 4% risk of LR in the 115 patients with adequate surgical margins, but a poor response to chemotherapy.

The outcome for patients with LR was poor, although not all died. Five of the 16 patients are long-term survivors (median 5.8 years from LR) after excision of their LR, four by amputation and one by wide local excision and radiotherapy. Only one was given second-line chemotherapy.

After LR, 11 of the patients have died, but survived a median of 12 months. All developed metastases. One was already known to have metastases before the diagnosis of LR, two had them synchronously with the LR and the other eight developed metastases a maximum of ten months after their LR (mean 7.5 months). Of these 11 patients, six had amputations for LR and two had local excision and radiotherapy. The only significant factor for survival after LR was the absence of metastases within one year of the LR. The disease-free interval from initial surgery to LR was not significant, nor was the method of management of the LR.

Metastatic disease. This developed in 102 patients at a mean of 15 months after the original diagnosis. No patient developed either metastases or LR after 49 months in this study. Of the 90 patients who developed metastases alone without LR, there was a survival rate of only 10% at more than five years after the diagnosis of metastases. The median survival time after the diagnosis of metastases was 12 months. There were no specific prognostic factors identified and a disease-free interval of over 24 months was not a significant predictor of outcome. The treatment of metastatic disease included surgery, chemotherapy, or a combination of these, as well as palliative measures. Although details of the number, location and size of the metastases were not obtained we observed a better survival for those who had received surgical excision and chemotherapy as opposed to other treatments.

Poor responders. We also compared the survival of a subgroup of patients with a poor response to chemotherapy and who had received limb-salvage surgery with marginal margins, with all patients who had undergone amputation (Fig. 3). This was to establish whether there was any best option for patients who were not responding well to chemotherapy, and for whom limb salvage would necessarily mean close margins. Neither group of patients did well and, although there was an initial trend for patients with limb

salvage to do better, by five years there was no significant difference between the two groups. This was despite the fact that nine of the 24 patients with limb salvage had developed LR compared with none of the 48 who had undergone amputation.

Pathological fracture. Of the 13 patients who presented with pathological fractures, six were treated by amputation and seven by limb salvage. Although only one of nine had over 90% necrosis on histological assessment, there were no LRs. Pathological fracture was not found to be a risk factor for survival or for local recurrence.

Discussion

One of the aims of our analysis has been to identify patient and surgical factors which can influence decision-making and survival. All our patients had been treated as part of a randomised trial of chemotherapy. Although two types of chemotherapy were administered the survival was no different between the two arms. Consequently, for the purposes of this study, the patients were considered to be a homogeneous group.⁸

We have, intentionally, used only the patients from the three largest surgical centres in the study since more data were collected than were required for the trial. The surgical decisions varied between the centres and depended upon the attitudes in those centres. No attempt was made to influence this, except to stress the importance of an adequate oncological procedure being carried out whenever possible.

The patients received neoadjuvant chemotherapy and underwent surgical resection after seven to nine weeks of drug treatment. The claimed advantage of neoadjuvant chemotherapy is not only the immediate treatment of tumour micrometastases, but also the ability to 'shrink' the primary tumour. This can make tumour margins more definable and simplify surgery. In practice this did not always occur. There were eight cases in which amputation had been planned, but limb salvage proved to be possible because of the benefit of neoadjuvant chemotherapy. By contrast, in 22 patients the tumour became inoperable and

required amputation. This group did badly, but no worse than others who had a planned amputation.

The most obvious difference between the three centres was seen in the rate of LR, which varied from 2.5% to 13.3%. This cannot be explained by a different chemotherapeutic response of the tumours at one centre, but appears to be related more to the surgical margins which were achieved. The centre with the lowest rate of LR had a very high (51%) rate of amputation or rotationplasty compared with the other two centres. It would appear that there is a 10% lower incidence of LR in group A, but a 35% higher chance of having an initial amputation or rotationplasty. This improved rate of LR did not translate into an improved overall survival. The survival curves for patients receiving an amputation at all three centres were virtually identical. This information supports Simon et al⁵ and Rougraff et al⁶ who showed previously a 10% excess of LR in limb-salvage patients, but did not associate this with poorer survival. The absence of LR in the group of rotationplasties confirms the safety of this procedure for obtaining local control in poor responders with large tumours. Our study does not exclude the possible significance of LR as a poor prognostic factor if it is analysed as a time-dependent variable, but this was outside the scope of this paper.¹²

This study has also confirmed previous work identifying risk factors for LR. Margins of excision and chemotherapy necrosis have been consistently found to be important (Table III). We have shown that a tumour volume of over 500 ml was also a risk factor in the 27% of patients with tumours of this size.

Picci et al¹³ undertook a detailed analysis of risk factors for LR after limb-salvage surgery and showed that, in almost every case, there is an identifiable factor which leads to a LR. They concluded that it is essential for the surgeon to consider wider margins if the response to pre-operative chemotherapy does not appear to be good.¹⁴ Although endorsing this, it would lead to increased numbers of amputations and our data have not supported the benefit of this in terms of overall survival.

The treatment of recurrent disease in osteosarcoma is also controversial. It is generally accepted that surgery is

Table III. Details from the literature of factors thought to be significant for local recurrence

	Margins (p value)	Length of neoadjuvant chemotherapy (p value)	Necrosis (p value)	Tumour size (p value*)	Limb salvage versus amputation	Incidence of local recurrence (%)
Delepine et al ¹⁹	<0.01	<0.00001	<0.01			17.0
Bielack et al ²⁰			0.012	NS	p = 0.012	4.8
Bacci et al ²¹	<0.0001		0.001	NS	NS*	5.7
Picci et al ²²	Yes				23 of 365 v 3 of 126	4.5
Bramwell et al ⁷					NS	6.9
Enneking and Kagan ²³	Yes					
Glasser et al ²⁴					9.2% v 1.9%	6.5
Brosjö ²⁵					11% v 2%	7.4
Ferrari et al ²⁶	<0.001		0.147			5.0
Sluga et al ²⁷					4.3% v 1.2%	2.3
Our study	<0.0001		0.07	0.003	13% v 0%	8.0

* NS, not significant

the mainstay of treatment. For LR, amputation is not always necessary and, if adequate surgical margins can be achieved, a wide excision followed by radiotherapy would appear to be a reasonable option.

The treatment of metastatic disease is also surgical. The role of second-line chemotherapy is controversial and in this group was used variably. The outcomes were very different and, although the only survivors were in those patients who had both complete surgical clearance and further chemotherapy, this did not reach statistical significance. Most authors have been unable to prove the benefits of chemotherapy in conjunction with thoracotomy,¹⁵ although more recent papers have shown survival for three years in up to 61% with combination treatment.^{16,17} There is clearly scope for a randomised study to answer this question.

The overall survival of the 202 patients in this subgroup was identical to that in the main EOI trial. This survival rate is lower than that from single institutions, but little different to that obtained in multi-institutional randomised trials. The role of the randomised trial for osteosarcoma has been questioned and confirmed as being essential. The reasons for the lower survival rates have been discussed and include factors such as a lower dose intensity of chemotherapy and patient selection.¹⁸

Chemotherapy remains the chief factor in curing patients and every attempt should be made to increase its efficacy. The disappointing fact that only 14% of these patients had over 90% necrosis, despite preoperative chemotherapy for seven to nine weeks, clearly indicates that there is scope for improvement. The response to chemotherapy is the only factor of significance, both in obtaining local control and in improving survival. It appears that clinical impressions of response are just as good as histopathological assessment. Surgical excision remains essential for local control. If limb-salvage surgery is attempted in unfavourable conditions (i.e., a poor response to chemotherapy and close margins) there is a greater than 30% risk of LR. On crude analysis there does not appear to be either an advantage or disadvantage to survival by performing an amputation at the time of the primary surgery.

The surgical treatment of osteosarcoma remains challenging and the importance of clinical trials, specialist centres, and the collection of data cannot be overemphasised.

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References

1. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med* 1986;314:1600-6.
2. Meyers PA, Heller G, Healey J, et al. Chemotherapy for non-metastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol* 1992;10:5-15.
3. Winkler K, Beron G, Kotz R, et al. Neoadjuvant chemotherapy for osteogenic sarcoma: results of a cooperative German/Austrian study. *J Clin Oncol* 1984;2:617-24.
4. Provisor AJ, Ettinger LJ, Nachman JB, et al. Treatment of non-metastatic osteosarcoma of the extremity with preoperative and post-operative chemotherapy: a report from the Children's Cancer Group. *J Clin Oncol* 1997;15:76-84.
5. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. *J Bone Joint Surg [Am]* 1986;68-A:1331-7.
6. Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. 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]* 1994;76-A:649-56.
7. Bramwell VHC, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992;10:1579-91.
8. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimes of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997;350:911-7.
9. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop* 1980;153:106-20.
10. Kaplan EL, Meier P. Nonparametric observations from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
11. Cox DR. Regression models and life tables. *J Roy Stat Soc* 1972;34:187-220.
12. Weeden S, Grimer RJ, Cannon SR, Taminiau AM, Uscinska BM. The effect of local recurrence on survival in resected osteosarcoma. *Eur J Cancer* 2001;37:39-46.
13. Picci P, Sangiorgi L, Bahamonde L, et al. Risk factors for local recurrences after limb-salvage surgery for high-grade osteosarcoma of the extremities. *Ann Oncol* 1997;8:899-903.
14. Picci P. Osteosarcoma: relationship of response to preoperative chemotherapy and type of surgery to local recurrence. *J Clin Oncol* 1994;12:2699-705.
15. Carter SR, Grimer RJ, Sneath RS, Matthews HR. Results of thoracotomy in osteogenic sarcoma with pulmonary metastases. *Thorax* 1991;46:727-31.
16. Saeter G, Hoie J, Stenwig AE, et al. Systemic relapse in osteogenic sarcoma: prognostic factors for long term survival. *Cancer* 1995;75:1084-93.
17. Antunes M, Bernardo J, Salete M, et al. Excision of pulmonary metastases of osteogenic sarcoma of the limbs. *Eur J Cardiothorac Surg* 1999;15:592-6.
18. Blum RH. Simplified vs complex adjuvant chemotherapy schedule for osteosarcoma. *Lancet* 1997;350:900-1.
19. Delepine N, Delepine G, Alkallaf S et al. Prognostic factors for local relapses following sparing surgery for osteosarcoma. 2nd Osteosarcoma Research Conference, Bologna, Italy 1996:140.
20. Bielack S, Kempf-Bielack B, Winkler K. Osteosarcoma: relationship of response to preoperative chemotherapy and type of surgery to local recurrence. *J Clin Oncol* 1994;12:2699-705.
21. Bacci G, Ferrari S, Mercuri M, et al. Predictive factors for local recurrence in osteosarcoma: 540 patients with extremity tumors followed for minimum 2.5 years after neoadjuvant chemotherapy. *Acta Orthop Scand* 1998;69:230-6.
22. Picci P, Sangiorgi L, Bahamonde L, et al. Risk factors for local recurrences after limb-salvage surgery for high-grade osteosarcoma of the extremities. *Ann Oncol* 1997;8:899-903.
23. Enneking WF, Kagan A. The implications of "skip" metastases in osteosarcoma. *Clin Orthop* 1975;111:33-41.
24. Glasser DB, Lane JM, Huvos AG, Marcove RC, Rosen G. Survival, prognosis and therapeutic response in osteogenic sarcoma: the Memorial Hospital experience. *Cancer* 1992;69:698-708.
25. Brosjo O. Surgical procedures and local recurrence in 223 patients treated 1982-1997 according to two osteosarcoma chemotherapy protocols: the Scandinavian Sarcoma Group experience. *Acta Orthop Scand Suppl* 1999;285:58-61.
26. Ferrari S, Bacci G, Picci P, et al. Long-term follow-up and post-relapse survival in patients with non-metastatic osteosarcoma of the extremity treated with neoadjuvant chemotherapy. *Ann Oncol* 1997;8:765-71.
27. Sluga M, Windhager R, Lang S, et al. Local and systemic control after ablative and limb sparing surgery in patients with osteosarcoma. *Clin Orthop* 1999;358:120-7.