OSTEOGENIC SARCOMA IN CHILDREN
A RETROSPECTIVE STUDY OF 58 CASES

M. MESKENS*, A. BURSSENS*, M. HOOGMARTENS*, G. FABRY*

Fifty-eight children between age 6 and 18 years were treated for osteogenic sarcoma in the period 1962 to 1987. Fifty-one patients with no preoperative pulmonary metastases (group A) had an overall 5-year survival rate (T5) of 41% ; they were subdivided into three subgroups. In subgroup A_1 treated with surgery and/or radiotherapy (15 cases), the 5-year survival rate (T5) was 33.3%, as in the classical historical series. In subgroup A_2 treated wth surgery and postoperative chemotherapy (19 cases) the T5 was 38.8%. In subgroup A_3 treated by surgery and pre- and postoperative chemotherapy (17 cases) the T5 was 66.6%, which was statistically the best therapy ($p < 0.5$). This confirms the general trend in orthopedic oncology. Further data proved the negative prognostic value of male sex, while the grade of tumor and the surgical margins were important factors, but not statistically significant. Seven patients with preoperative metastases (group B) had a T5 of 0%.

Keywords : osteogenic sarcoma ; pediatric ; chemotherapy ; survival rate ; prognostic factors.
Mots-clés : sarcome ostéogénique ; pédiatrique ; chimiothérapie ; survie ; facteurs pronostiques.

INTRODUCTION

Osteogenic sarcoma is a neoplasm with proliferating malignant cells, producing either osteoid substance or material histologically indistinguishable from it in at least small foci (1). This tumor, often seen in young patients between age 15 and 25 years, is one of the most frequent primary bone sarcomas. The prognosis of this tumor, if left untreated, is very limited. The 5-year survival rate after aggressive surgery alone averages only 20 to 30% (7). Since the introduction of chemotherapy and especially the combination of surgery and pre- and postoperative chemotherapy the prognosis has improved to a 5-year survival of 50 to 60% (7). Patients treated now by surgery and pre- and postoperative chemotherapy have a strong chance of surviving 5 or 10 years (4, 7). Moreover, many orthopedic surgeons preserve function by performing limb-saving surgery without compromising the survival rate (5, 6).

In fact there are two major goals in the treatment of these patients : control of the primary lesion and of possible metastases, thus providing long-term survival and maintenance of function.

This paper presents the results of a retrospective follow-up of 58 cases of osteogenic sarcoma in children between 6 and 18 years, treated in the period 1962 to 1987. Factors of prognostic value are also studied.

METHODS

Fifty-eight patients between age 6 and 18 years were studied. All patients were routinely screened for metastatic spread before therapy. This was first done by plain radiographs of the chest and tomography of the lungs, and later on by CT scans of the lungs. Technetium scintigraphy was performed in every patient.

* Department of Orthopedic Surgery, University Hospital, B-3212 Pellenberg, Katholieke Universiteit Leuven, Belgium.
Correspondence and reprints : M. Meskens.

The patients were divided into two groups, A and B, according to whether or not they had metastases at their first visit.

Group A (table I) consisted of 51 patients (88%) without initial pulmonary metastases. The male/female ratio (M/F) was 28/23 ; the distribution between left and right (L/R) was 26/25 (table I). The age averaged 15 years with a minimum of 6 years and a maximum of 18 years. The primary lesion was located in the distal part of the femur in 33 patients (table I), in the proximal humerus in 6, in the proximal tibia in 4, in the distal tibia in 3, in the proximal fibula in 2, and in the pubis, the femoral shaft and the tibial shaft in one patient each.

All the lesions were classified according to Enneking (2, 3) : one patient had a grade Ia tumor, 6 had a grade IIa tumor, and 44 had a grade IIb tumor.

In group A, 15 patients (subgroup A1) (table II) were treated with surgery and/or radiation therapy, without any form of chemotherapy. Six of these were treated by surgery (amputation or disarticulation) alone, 7 by a combination of surgery (amputation or disarticulation) and radiotherapy, and 2 by radiotherapy alone.

Nineteen patients (subgroup A2) (table II) were treated by surgery (amputation or disarticulation) and postoperative chemotherapy. Nine received the COM-

Table I. — Clinical material

	Group A (without metastases)	Group B (with metastases)
1. Anatomical distribution of the lesions :		
Distal femur	33	3
Proximal humerus	6	2
Proximal tibia	4	1
Distal tibia	3	1
Proximal fibula	2	
Pubis	1	
Shaft of the femur	1	
Shaft of the tibia	1	
	51	7
2. Sex ratio (M/F)	28/23	5/2
3. Left/right	26/25	3/4
4. Staying	Ia = 1 Ib = 0 IIa = 6 IIb = 44	III = 7

Table II. — Treatment modalities

Group A	(without preoperative metastases) n = 51 (T5 : 41.0%)
Subgroup A1	surgery and/or radiotherapy : n = 15 (T = 33.3%) 1. surgery alone : n = 6 2. surgery + radiotherapy : n = 7 3. radiotherapy alone : n = 2
Subgroup A2	surgery and postoperative chemotherapy : n = 19 (T5 = 38.8%) 1. Compadri : n = 9 2. Vincristine, doxorubicin, cyclophosphamide : n = 10
Subgroup A3	surgery and pre- and postoperative chemotherapy : n = 17 (T5 = 66.6%) 1. Rosen T10 : n = 10 2. Vincristine, doxorubicin, cyclophosphamide : n = 7
Group B	(with preoperative metastases) n = 7 (T5 : 0%) 1. no therapy : n = 1 2. radiotherapy alone : n = 1 3. preoperative radiotherapy and surgery : n = 2 4. preoperative radiotherapy, surgery and postoperative chemotherapy (doxorubicin and cyclophosphamide) : n = 1 5. surgery and pre- and postoperative chemotherapy : n = 2, of which Rosen T10 : n = 1 Vincristine, doxorubicin, cyclophosphamide : n = 1

PADRI I scheme (cyclophosphamide, vincristine, PAM and doxorubicin), and 10 patients a combination of vincristine, doxorubicin and cyclophosphamide.

Seventeen cases (subgroup A3) (table II) were treated by surgery (amputation or disarticulation) and preoperative and postoperative chemotherapy. Ten patients received the T10 scheme of Rosen, and 7 were treated by vincristine, doxorubicin and cyclophosphamide. Other drugs were added in case of poor response to the preoperative chemotherapy.

Group B (table I) consisted of 7 patients (12%) with pulmonary metastases before the onset of therapy. The sex ratio (M/F) was 5/2 and the distribution between left and right (L/R) was 3/4. The age averaged 12 years. Three lesions were localized in the distal femur, two in the proximal humerus and one in the proximal tibia and the distal tibia each. They were all grade III lesions according to Enneking. One patient refused therapy (table II). One patient was treated by radiotherapy of the primary tumor alone. Five patients were treated by surgery (amputation or disarticulation) : in two cases the surgery was combined with preoperative radiotherapy, in one case surgery was combined with preoperative radiotherapy and postoperative chemotherapy (doxorubicin and cyclophosphamide), and in 2 cases surgery was combined with pre- and postoperative chemotherapy (in one case the Rose T10 scheme and in the other case vincristine, doxorubicin and cyclophosphamide).

Because sample proportions were compared, the standardized variable was calculated to test the null hypothesis that there was no difference between the population parameters (Student's t test ; one-tailed test of significance).

RESULTS

Group A (table II) consisted of 51 patients without preoperative metastases in the lungs. The survival rate after 5 years (T5) averaged 41.0%.

In subgroup A1 (surgery and/or radiotherapy without chemotherapy) the T5 was 33.3%, in subgroup A2 (surgery and postoperative chemotherapy) the T5 was 38.8% and in subgroup A3 (surgery and pre- and postoperative chemotherapy) the T5 was 66.6% (fig. 1).

Metastases, skip lesions and local recurrences were specifically studied in group A.

Thirty-two patients or 62.7% developed pulmonary metastases after a mean interval of 10 months from the onset of therapy. In 10 cases one or more thoracotomies were performed, and the T5 for these 10 patients averaged 28.5%. It must be mentioned however that with regard to the long-term follow-up of the patients after thoracotomy only one patient remained alive and disease-free, one patient was alive but with metastases, while the 8 others died. Twenty-two patients in whom no surgery for metastases was performed had a poor outcome : none of them survived 5 years.

Two patients (3.9%) with osteogenic sarcoma of the distal femur were found to have skip metastases higher up in the femur. They were both treated by a disarticulation of the hip (a radical margin). In one of them the surgery was combined with postoperative chemotherapy but the patient survived only 13 months. In the other patient the surgery was combined with pre- and postoperative

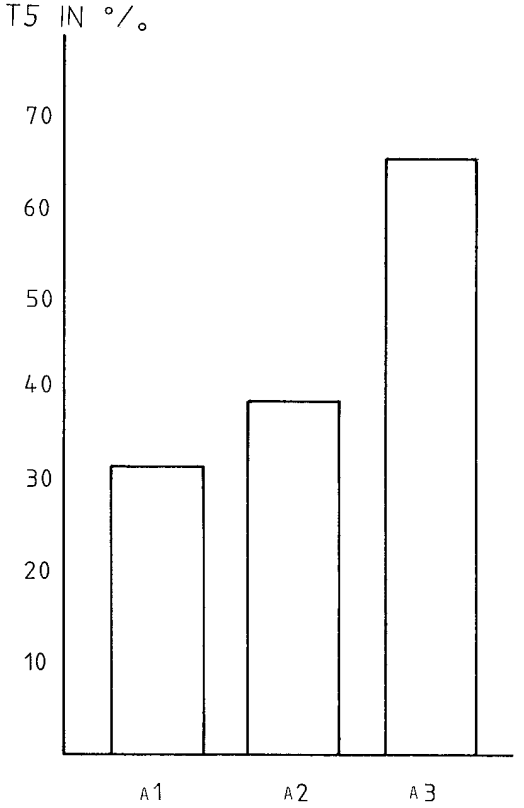

Fig. 1. — Relation between 5-year survival (T5) and treatment modalities in group A (without preoperative metastases).
1. Subgroup A1 : surgery and/or radiotherapy : T5 = 33.3%.
2. Subgroup A2 : surgery and postoperative chemotherapy : T5 = 38.8%.
3. Subgroup A3 : surgery and pre- and post-operative chemotherapy : T5 = 66.6%.

chemotherapy, and he died after 26 months because of pulmonary metastases.

Local recurrence was noted in 3 patients (5.8%), unrelated to the presence of skip metastases. One of these had a primary lesion in the distal femur, treated by an above-knee amputation and postoperative chemotherapy. She developed a stump recurrence, which was treated by disarticulation of the hip, but she died after 34 months. The second patient had an osteogenic sarcoma of the proximal humerus treated by preoperative radiotherapy and a forequarter amputation. The patient developed a local recurrence treated by local resection, but he died after 16 months. The third patient had a grade Ia lesion of the tibial shaft, treated surgically with an intralesional margin. The recurrence was treated by an above-knee amputation, and the patient was still alive after 10 years.

Three unfavorable variables were studied in group A : male sex, advanced surgical stage, and insufficient surgical margin.

The T5 of the 23 girls was 52.6% ; the T5 of the 28 boys was 30.0% (fig. 2) ($p < 0.05$).

The patient with the Ia lesion was still alive after 10 years. For the 6 patients with grade IIa lesions the T5 was 66.6%, and for the 44 cases with grade IIb lesions the T5 was 34.4% ($p > 0.05$, or not significant).

Surgery was carried out in 49 patients. The margin obtained at surgery was intralesional in 1 case, wide in 9 cases and radical in 39 cases. The patient with the intralesional margin at the tibial level developed a local recurrence, which was treated with an above-knee amputation ; he was still alive after 10 years. For the 9 patients treated by a wide resection the T5 was 25%, and for the 39 treated by a radical margin the T5 was 43.7% ($p > 0.05$, or not significant).

Group B (table II) consisted of 7 patients with lung metastases when they were first seen in the outpatient clinic. The longest survival was 34 months, with an average of 12 months for the whole group (T5 = 0%). A metastasectomy was performed in one case, 17 months after treatment with amputation and pre- and postoperative chemotherapy, but the patient survived only 34 months.

DISCUSSION AND CONCLUSION

The survival of the patient is the most important objective of the surgeon treating osteogenic sarcoma. The positive influence of chemotherapy and especially the combination of pre- and postoperative chemotherapy on the survival rate was quite obvious in this series (table II). In 17 patients without pulmonary metastases treated by surgery and pre- and postoperative chemotherapy the T5 averaged 66.6%, whereas the T5 was only 33.3% in 15 patients without pulmonary metastases and treated only by surgery or/and radiotherapy. In other words, surgery with pre- and postoperative chemotherapy was the best treatment ($p < 0.05$). This confirms a general trend (4).

Some factors like youth, male sex, brief duration of symptoms, osteoblastic subtype and large tumor volume are known to have an unfavorable prognostic value (7). In this series a statistically significant ($p < 0.05$) influence of sex on the survival rate was noted : in group A the outcome was better in girls (fig. 2). A correlation

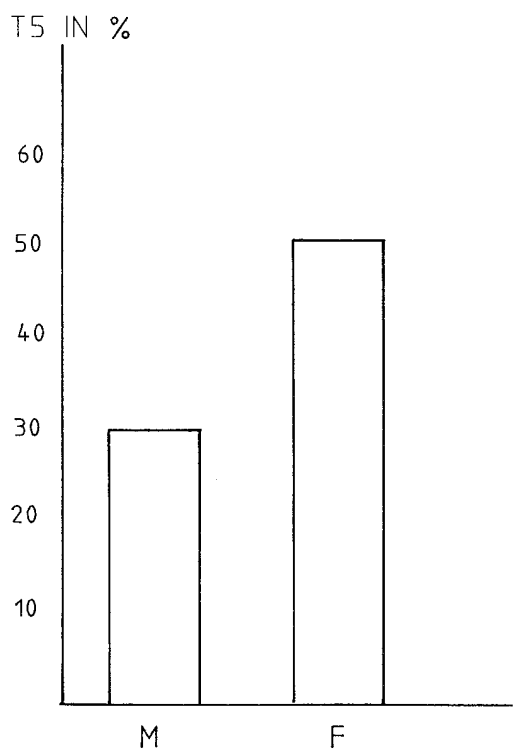

Fig. 2. — Relation between sex and 5-year survival (T5).
M. (Male) : T5 = 30%.
F. (Female) : T5 = 52.6%.

(but not statistically significant) was also found between the grade of the tumor and the outcome. For IIa lesions the T5 was 66.6%, for IIb lesions the T5 was 34.3%, and for grade III lesions the T5 was 0%. A similar correlation (but not statistically significant) was found for surgical margin. For other factors like age and anatomical localization of the tumor, the relation was less obvious, probably because of the small number of patients in each subgroup.

A thoracotomy was performed in 11 cases, and only one patient remained alive and disease free.

Acknowledgements

The authors wish to express their appreciation to Jos Nijs for his assistance with statistical methods.

REFERENCES

1. Dahlin D. C., Unni K. K. Bone tumors. General aspects and data on 8542 cases. Charles C. Thomas, Springfield, 1986, 269-307.
2. Enneking W. F., Spanier S. S., Goodman M. A. Current concepts review. The surgical staging of musculoskeletal sarcoma. J. Bone Joint Surg., 1980, 62-A, 1027-1030.
3. Enneking W. F., Spanier S. S., Goodman M. A. A system for the surgical staging of musculoskeletal sarcoma. Clin. Orthop., 1980, 153, 106-120.
4. Rosen G. Neoadjuvant chemotherapy for osteogenic sarcoma. In : Limb salvage in musculoskeletal oncology, Churchill Livingstone, New York, 1987, 260-268.
5. Sim F. H., Wold L. E., Beabout J. W., Amandio P. C., McDonald D. J. Osteosarcoma : state of the art. Minnesota Medicine, 1986, 69, 442-448.
6. Springfield D. S., Schmidt R., Graham-Pole J., Marcus R. B., Spanier S. S., Enneking W. F. Surgical treatment for osteosarcoma. J. Bone Joint Surg., 1988, 70-A, 1124-1130.
7. Taylor W. F., Ivins J. C., Pritchard D. J., Dahlin D. C., Gilchrist G. S., Edmondson J. H. Trends and variability in survival among patients with osteosarcoma : a 7-year update. Mayo Clin. Proc., 1985, 60, 91-104.

SAMENVATTING

M. MESKENS, A. BURSSENS, M. HOOGMARTENS en G. FABRY. Osteogeen sarcoom bij het kind. Een retrospectieve follow-up studie van 58 gevallen.

In de periode 1962-1987 werden 58 patiënten tussen 6 en 18 jaar behandeld voor osteogeen sarcoom. Hiervan hadden 51 (groep A) geen longmetastasen bij de eerste raadpleging ; hiervan overleefden 41% na 5 jaar (T5 : 41%). Genoemde groep van 51 werd verdeeld in drie ondergroepen. In ondergroep A_1 behandeld met heelkunde en/of radiotherapie (15 gevallen) was de T5 33.3%, ongeveer zoals in de klassieke historische series. In ondergroep A_2 behandeld met heelkunde en postoperatieve chemotherapie (19 gevallen) was de T5 38.8%. In ondergroep A_3 behandeld met heelkunde en pre- en postoperatieve chemotherapie (17 gevallen) was de T5 66.6%, statistisch dus de beste therapie ($p < 0.5$). Dit bevestigt de algemene evolutie in de orthopedische oncologie. Prognostisch gezien was het mannelijk geslacht een statistisch significante negatieve factor, terwijl de graad van de tumor en de volledigheid van de resectie belangrijk waren, maar niet statistisch significant. Zeven patiënten hadden wel metastasen bij de eerste raadpleging (groep B) ; hun T5 was 0%.

RÉSUMÉ

M. MESKENS, A. BURSSENS, M. HOOGMARTENS et G. FABRY. Le sarcome ostéogénique chez l'enfant. Suivi rétrospectif de 58 cas.

Cinquante-huit malades, âgés de 6 à 18 ans, furent traités pour sarcome ostéogénique entre 1962 et 1987. Cinquante-et-un (groupe A) n'avaient pas de métastases pulmonaires à la première consultation ; 41% survivaient après 5 ans (T5 : 41%). Ce groupe de 51 fut divisé en trois sous-groupes. Dans le sous-groupe A_1 traité par chirurgie et/ou radiothérapie (15 cas) le T5 était 33.3%, comme dans les séries classiques. Dans le sous-groupe A_2 traité par chirurgie et chimiothérapie post-opératoire (19 cas) le T5 était 38.8%. Dans le sous-groupe A_3 traité par chirurgie et chimiothérapie pré- et post-opératoire (17 cas) le T5 était 66.6% ; cette combinaison serait donc statistiquement le traitement de choix ($p < 0.5$). Ceci confirme l'évolution générale dans l'oncologie orthopédique. D'un point de vue pronostique, le sexe masculin est un facteur péjoratif, statistiquement significatif, tandis que le stade de la tumeur et la perfection de la résection sont des facteurs importants, mais non statistiquement significatifs.
Sept malades avaient des métastases pulmonaires à la première consultation (groupe B) ; leur T5 était 0%.