ORIGINAL ARTICLE

Osteosarcoma in Preadolescent Patients: Experience in a Single Institute in Taiwan

Ming-Yun Hsieh[1,4], Giun-Yi Hung[2,4]*, Hsiu-Ju Yen[2,4], Wei-Ming Chen[3,4], Tain-Hsiung Chen[3,4]

[1]Department of Pediatrics, Far Eastern Memorial Hospital, Departments of [2]Pediatrics and [3]Orthopedics and Traumatology, Taipei Veterans General Hospital, and [4]National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Background: The incidence of osteosarcoma peaks in adolescence and is much lower in preadolescence. However, reports on its clinical features in preadolescent patients are conflicting. In this study, we attempted to assess the differences in clinical appearance and prognosis of the malignancy between preadolescent and adolescent patients.

Methods: Between January 1980 and January 2006, 13 preadolescent and 58 adolescent patients with high-grade osteosarcoma were treated at our institute, and their medical records were reviewed and compared.

Results: The sex distribution, primary metastasis rate, pathologic fracture, histologic type, primary tumor location, and percentage of high alkaline phosphatase level were not different between the 2 groups. Poor responders (tumor necrosis rate $<90\%$) were more common in the preadolescent group (80% *vs.* 43%, $p=0.035$). Overall survival rates in the preadolescent and adolescent groups were 51.3% and 56.4%, respectively ($p=0.735$). In patients without primary metastasis, the 5-year overall survival rates were 60.6% and 66.7% for 11 preadolescents and 39 adolescents, respectively ($p=0.925$).

Conclusion: Considering the common findings in both groups, we suggest that preadolescent patients should be treated with the same regimen as that used for adolescent patients. [*J Chin Med Assoc* 2009;72(9):455–461]

Key Words: adolescent, osteosarcoma, preadolescent

Introduction

High-grade osteosarcoma is the most common bone malignancy in children. Its incidence in this population varies significantly with age, with peak incidence occurring in the second decade of life during the adolescent growth spurt, a feature that suggests a relationship between rapid bone growth and the development of malignancy.

In children younger than 10 years, Ewing's sarcoma is more common than osteosarcoma,[1] and preadolescents amount to only a small proportion of patients with osteosarcoma. Because their physical status is distinct from that of adolescents, the pathophysiology of osteosarcoma development in this group might be different from that in adolescents. Thus far, reports on the clinical features among preadolescent patients have shown conflicting results; some reports suggest a poorer prognosis for preadolescent patients,[2–4] whereas others show no difference.[5–8] There are no reports of osteosarcoma in preadolescent patients in Taiwan. In this study, we observed 13 preadolescents with high-grade osteosarcoma treated at our hospital and compared the findings with those seen in 58 adolescent patients to assess the differences in prognosis and clinical appearance of the malignancy.

Methods

Patients

Between January 1980 and January 2006, 75 patients younger than 18 years received treatment for high-grade osteosarcoma at the Department of Pediatrics, Taipei Veterans General Hospital. Four adolescent patients were excluded because of incomplete medical records. Among the remaining 71 patients, 13 were preadolescents, defined as children younger than 10 years of age. Their clinical course was observed and the following data were collected: age, sex, primary

*Correspondence to: Dr Giun-Yi Hung, Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: gyhung@vghtpe.gov.tw • Received: January 5, 2009 • Accepted: August 21, 2009

metastasis or pathologic fracture, tumor location, alkaline phosphatase (ALP) level before treatment, type of surgery, tumor necrosis induced by chemotherapy, and survival outcome. High ALP level, which differs with age, was defined according to the Lockitch et al[9] report. Tumor necrosis rate was assessed by the pathologic reports, and good responders were defined as those with a necrosis rate ≥90% and poor responders as those with a necrosis rate <90%.

Diagnosis and follow-up

Osteosarcoma was diagnosed on the basis of tumor biopsy reports. For staging, all patients underwent chest X-rays, chest computed tomography (CT), and whole-body bone scanning. Primary lesion detection was carried out with X-ray and magnetic resonance imaging (MRI). All the examinations were repeated before definitive surgery. After surgery, chest and primary lesion X-rays, chest CT, and whole-body bone scanning were performed every 3 months throughout the period of adjuvant chemotherapy. After completion of the entire treatment course, all patients were followed every 3 months during the first 2 years, every 6 months for the following 3 years and then yearly thereafter.

Chemotherapy

Over the long study period (Table 1), the chemotherapy protocol changed but still included neoadjuvant and adjuvant chemotherapy. The preadolescent and adolescent patients were treated with the same protocol. Before May 2003, the chemotherapy protocol was unstratified, consisting of high-dose methotrexate, epirubicin, cisplatin and ifosfamide, with surgery performed at week 15. For intensification of chemotherapy, a new protocol, similar to the regimens from the Rizzoli Institute,[10] was adopted after May 2003. The new protocol increased the accumulative doses of cisplatin and ifosfamide, with decreased frequency of methotrexate usage, and substituted epirubicin with doxorubicin.

Postoperative adjuvant chemotherapy was stratified according to the tumor necrosis rate to avoid excessive chemotherapy in good responders. Good responders and poor responders received 2 and 3 cycles of the 4 drugs (high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide), respectively. In patients with primary metastasis or relapse, the same chemotherapeutic agents with a higher accumulative dose or other salvage chemotherapeutics were administered depending on the primary doctors' decision.

Surgery

Most patients underwent limb-salvage surgery instead of amputation when possible. The type of surgery depended on the location and extension of the tumor, neurovascular involvement, and the presence of complicating factors such as pathologic fracture. The type of reconstruction after tumor resection included the use of prosthesis, extracorporeally irradiated autograft-prosthetic composite arthroplasty,[11] reconstruction with autograft or allograft,[12] and allograft arthrodesis,[13] as previously reported.

Table 1. Patient characteristics and operation results of the 13 Taiwanese preadolescent patients with high-grade osteosarcoma

Patient # (yr of diagnosis)/ primary metastasis	Age (yr)/ sex	Primary site	ALP (U/L)	Histology	Traditional therapy/ duration of symptoms	Type of surgery	Necrosis rate (Grade)†
1 (1995)	8.7/M	Femur, D	418	Osteoblastic	NR/2 mo	Limb-salvage	NA
2 (1996)	9.5/M	Tibia, P	395	Osteoblastic	Yes/2 mo	Amputation	NA
3 (1997)	6.9/F	Femur, D	349	Osteoblastic*	NR/1 mo	Limb-salvage	NA
4 (1997)	7.0/F	Femur, D	212	Osteoblastic	NR/1 mo	Limb-salvage	II
5 (1999)/lung	8.3/F	Femur, D	228	Osteoblastic	Yes/1 mo	Limb-salvage	II
6 (2000)	6.4/M	Femur, D	583 (h)	Osteoblastic	Yes/2 mo	Amputation	II
7 (2001)	5.7/M	Femur, P	1,353 (h)	Osteoblastic	Yes/0.5 mo	Limb-salvage	I
8 (2002)/bone	8.8/F	Femur, D	302	Osteoblastic*	Yes/1 mo	Limb-salvage	IV
9 (2002)	5.5/M	Humerus, P	252	Telangiectatic	Yes/2.5 mo	Limb-salvage	II
10 (2003)	4.8/F	Tibia, P	470 (h)	Osteoblastic	Yes/1 mo	Limb-salvage	II
11 (2003)	9.2/M	Femur, D	1,619 (h)	Osteoblastic	Yes/2.5 mo	Limb-salvage	II
12 (2004)	8.7/M	Tibia, P	402	Osteoblastic	No/1 mo	Limb-salvage	III
13 (2005)	6.7/M	Tibia, P	195	Osteoblastic	NR/0.5 mo	Amputation	II

**With pathologic fracture; †necrosis rate induced by neoadjuvant chemotherapy (Grades I, II, III and IV indicate <10%, 10–90%, >90% and 100%, respectively). D = distal; P = proximal; h = high; NR = not reported.*

Statistical analysis

Overall survival was defined as the time from diagnosis of the tumor until death or last patient contact, whichever occurred first. The overall survival rates were measured using the Kaplan-Meier method and compared using the log-rank test between the groups. The differences between preadolescent and adolescent patients were examined using the χ^2 test or Fisher's exact test. A p value < 0.05 was considered to be statistically significant.

Results

Findings in the preadolescent patients

The preadolescent group comprised 8 males and 5 females. Their clinical features, treatment protocol, and outcome are summarized in Tables 1 and 2.[14,15] The median age was 7.0 years (range, 4.8–9.5 years). The osteoblastic type was the most common histologic type (12 patients), and the distal femur was the most common primary tumor location (7 patients). Two patients had pathologic fractures at diagnosis (patients 3 and 8), and 2 were considered to have primary metastasis (patients 5 and 8). The median ALP level at diagnosis was 395 U/L (range, 195–1,619 U/L). In 11 patients without primary metastasis, the median ALP level was 402 U/L (range, 195–1,619 U/L; Table 1). Four preadolescent patients had high ALP levels according to age-adjusted normal ranges.

All the 13 patients received chemotherapy and surgery; 12 received the entire treatment, of which 10 were treated with the pre-2003 protocol, and 2 received the new protocol. One patient (patient 4) received another

Table 2. Treatment and outcome of the 13 Taiwanese preadolescent patients with high-grade osteosarcoma

Patient # (yr of diagnosis)	Primary chemotherapy and reasons for protocol violation	Months to relapse (site)	Treatment at relapse	Survival (mo)/ outcome
1 (1995)	MCIE; early surgery due to tumor progression	41 (lung)	Wedge resection of lung, C/T, R/T over brain and lung, PBSCT (Reference 14)	53/D
2 (1996)	MCIE; amputation initially due to large tumor	–	–	134/NED
3 (1997)	MCIE	–	–	125/NED
4 (1997)	MCIE, VP16	13 (local)	Amputation, C/T, PBSCT	31/D
5 (1999)	MCIE; suspended C/T prematurely due to renal insufficiency and severe electrolyte imbalance	29 (lung)	Tumor excision and pneumolysis, C/T	30/D
6 (2000)	MCIE; amputation initially because of encasement of neurovascular bundle	–	–	86/NED
7 (2001)	MCIE	20 (L3 and retroperitoneum)	R/T, resection, C/T (cyclophosphamide, VP16, carboplatin)	78/free of disease
8 (2002)	MCIE	15 (humerus)	Resection, R/T, C/T (carboplatin, cyclophosphamide, MTX, ifosfamide, topotecan)	33.5/D
9 (2002)	MCIE; previously C/T 3 times at another hospital, substituted epirubicin for lipodox due to chest pain	–	–	60/NED
10 (2003)	MCIA, VP16; changed C/T after surgery due to poor tumor necrosis rate	10 (lung)	Multiple thoracotomies, C/T	31/D
11 (2003)	MCIEA; previously C/T once at another hospital	20 (ankle)	C/T (MCIE, VP16), R/T	32.5/D
12 (2004)	MCIA; ifosfamide induced acute pancreatitis twice, reduced ifosfamide dosage (Reference 15)	–	–	37/NED
13 (2005)	MCIA; refused C/T initially, tumor progressed, amputation 1 mo later	–	–	34/NED

MCIEA = methotrexate, cisplatin, ifosfamide, epirubicin, adriamycin; VP16 = etoposide; C/T = chemotherapy; R/T = radiotherapy; PBSCT = autologous peripheral blood stem cell transplant; D = died of disease; NED = no evidence of disease.

chemotherapy regimen (TPOG-OS94 protocol)[16] before she was referred to our hospital for surgery after local recurrence. Patient 10 was the only one unable to complete the scheduled chemotherapy because of pulmonary metastases during adjuvant chemotherapy, and alternative chemotherapy was adopted subsequently.

Three patients underwent amputation because of large tumor size, involvement of neurovascular bundles, and aggressive tumor progression despite coadministration of chemotherapy. The other 10 patients underwent limb-salvage surgery; 5 received arthrodesis and 1 (patient 3) underwent a lengthening operation for leg discrepancy after skeletal maturity. The tumor necrosis rate induced by neoadjuvant chemotherapy was evaluated in 10 patients, with only 2 showing a good histologic response.

Two of the 13 patients had primary metastasis (Table 1, patients 5 and 8). Patient 5 had a solitary subpleural nodule that disappeared temporarily on the chest CT after chemotherapy. However, 18 months after completing the entire chemotherapy regimen, lung metastasis occurred and was pathologically proven by wedge resection. Patient 8 had bone metastasis over the left proximal humerus, which was initially revealed by a bone scan. It was not determined by the first biopsy during the limb-salvage surgery and was discovered 11 months later when a painful swelling developed and rebiopsy was performed. Of the remaining 11 patients, 5 relapsed; 2 had lung metastases, 1 had local recurrence, and 2 developed bone metastases (Table 2). The therapy regimens for the 7 patients with metastasis or relapse are shown in Table 2.

All the 7 patients received chemotherapy, 6 underwent surgery for tumor removal, 4 received palliative radiation for local control, and 2 received high-dose chemotherapy with an autologous peripheral blood stem cell transplant (PBSCT). Despite the aggressive salvage therapy, 6 patients died, and only patient 7 survived without evidence of disease. The causes of death were tumor progression in 5 patients and metastatic intestinal tumor complicated with intussusception and septic shock in 1 patient (Table 2).[14]

The median follow-up duration for the preadolescent patients was 37 months (range, 30–134 months). The 5-year overall survival rate was 51.3% for all the patients and 60.6% for the 11 patients without primary metastasis (Figures 1 and 2).

Comparison with the adolescent patients

The adolescent group consisted of 39 males and 19 females, with a median age of 13.8 years (range, 10.1–17.9 years). The sex distribution indicated more common tumor occurrence in males, as in the preadolescent group (p=0.751; Table 3). Primary metastasis was diagnosed in 19 patients, which was not statistically different from the preadolescent patients (32.8% *vs.* 15.4%, p=0.319). The most common tumor location and histologic types were distal femur and osteoblastic type, respectively, in both groups (Table 3). Thirty-five patients received the pre-2003 protocol and 15 received the new protocol. Data on the tumor necrosis rate induced by neoadjuvant chemotherapy were available for 42 (72.4%) patients, and 24 (57%) of these patients were good responders. Good responders were more common in the adolescent group (57% *vs.* 20%, p=0.035). The median ALP level was 280 U/L (range, 87–2,584 U/L). The percentage of high ALP was not different from that of the preadolescent patients (25% *vs.* 30.8%, p=0.728). The same results applied to

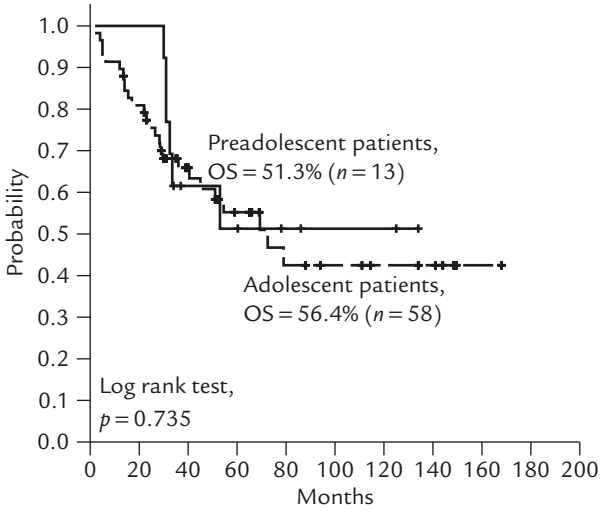

Figure 1. Kaplan-Meier plot of overall survival (OS) in preadolescent and adolescent patients.

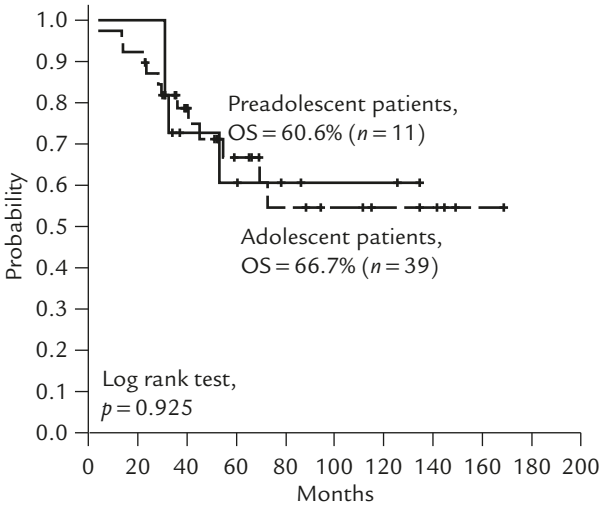

Figure 2. Kaplan-Meier plot of overall survival (OS) in patients without primary metastasis.

Table 3. Comparison of patient characteristics between preadolescent and adolescent patients*

	Preadolescents ($n=13$)	Adolescents ($n=58$)	p
Age (yr)	4.8–9.5	10.1–17.9	
Sex			0.751
Male	8 (62)	39 (67)	
Female	5 (38)	19 (33)	
Pathologic fracture			0.633
Yes	2 (15)	6 (10)	
No	11 (85)	52 (90)	
Traditional therapy before diagnosis			0.425
Yes	8 (89)	30 (73)	
No	1 (11)	11 (27)	
Not reported	4	17	
ALP			0.728
High	4 (31)	12 (25)	
Normal	9 (69)	36 (75)	
Not reported		10	
Tumor necrosis rate			0.035
≥ 90%	2 (20)	24 (57)	
< 90%	8 (80)	18 (43)	
Not reported	3	16	
Histologic type			0.256
Osteoblastic	12 (92)	41 (76)	
Non-osteoblastic	1 (8)	13 (24)	
Not reported		4	
Tumor location			0.925
Distal femur	7 (54)	26 (45)	
Proximal tibia	4 (31)	19 (33)	
Humerus	1 (7.5)	7 (12)	
Others	1 (7.5)	6 (10)	
Amputation			0.353
Yes	3 (23)	6 (11)	
No	10 (77)	51 (89)	

**Data presented as range or n (%). ALP = alkaline phosphatase.*

the incidence of pathologic fracture (6 of 58 patients, $p=0.35$) and the rate of amputation (6 of 57 patients, $p=0.633$). The median survival time in the adolescent group was 39 months (range, 2–168 months), and the 5-year survival rate was 56.4%. The 5-year survival rate in the adolescent patients without primary metastasis was 66.7% (Figures 1 and 2). Compared with the 51.3% for all the preadolescent patients and the 60.6% for the preadolescent patients without primary metastasis, no survival difference was found between the groups ($p=0.735$ and $p=0.925$).

Discussion

This retrospective study compared the clinical characteristics and outcome of osteosarcoma between 13 preadolescent and 58 adolescent patients. No differences were observed between the groups in terms of tumor location, histologic type, primary metastasis, pathologic fracture, and high ALP level at presentation. The only difference was a higher number of good responders to chemotherapy in the adolescent group. The 5-year survival rates between the groups were similar. The survival rates of 60% and 70%, respectively, in the latest large-scale study from the Rizzoli Institute,[8] comparing 133 preadolescent patients and 782 older patients (13–40 years old), were essentially the same as our results. This report also described a higher incidence in females and more non limb-salvage surgeries for preadolescent patients. However, our study found a higher incidence in male preadolescents, as in adolescent patients and in other reports.[5,6,17] Differences in race or inherent tumor properties among

preadolescent patients are possible explanations, and further studies are necessary to arrive at a suitable conclusion. With regard to limb-salvage surgery, this procedure is especially challenging for preadolescent patients because it results in unacceptable leg discrepancy. Although not statistically significant, the amputation rate for our preadolescent patients was also higher than that for the adolescent patients (23% *vs.* 11%). Compared with the 11% amputation rate in the Cho et al[6] study, 58% in the Rytting et al[7] study, and 23% in the Bacci et al[8] study, our results do not show an especially high amputation rate in preadolescent patients. Among the 10 preadolescent patients who underwent limb-salvage surgery, 6 died of tumor relapse, 1 had not reached final skeletal maturity, 2 underwent surgery without destroying the growth plate, and 1 underwent a lengthening operation for leg discrepancy. Despite the high relapse rate (6 of 10) among patients who underwent limb-salvage surgery, local recurrence was not the main cause of relapse. With advances in surgical techniques, including expansion procedures,[18] and functional and cosmetic preservation for long-term survivors,[19] the use of limb-salvage surgery in preadolescent patients will increase in the future.

Our study showed a higher number of poor responders among the preadolescent (80%) than adolescent patients (43%, $p = 0.035$), which has not been observed before. The rate of 80% poor responders in the preadolescent group is similar to the 68% reported by Cho et al,[6] but inferior to the 37% reported by Bacci et al.[8] One possible explanation is the different tumor biology. Another explanation is the intensity of chemotherapy, which was weaker before 2003, and most of the preadolescent patients (10 of 13) in this study received the pre-2003 protocol. The chemotherapy regimens administered by Bacci et al[5,8] in the Rizzoli Institute were also stronger than those administered by Cho et al.[6] Moreover, the finding that the survival rate was not poor even with the poor responders in the preadolescent group is interesting. Lewis et al[20] reported an improved histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy. Eselgrim et al[21] found that higher doses of preoperative chemotherapy do not increase the tumor necrosis rate or improve final survival. Because of the lower patient numbers and insufficient follow-up time after the new protocol, we could not prove that intensification and stratification of chemotherapy according to tumor necrosis rate can improve survival, even though we observed a better tumor necrosis rate after the use of the new protocol. Therefore, although the tumor necrosis rate has been documented as a prognostic factor in many studies,[6,22–24] its role as a surrogate outcome measure in protocols requires further study. Moreover, the pathologic assessment of the tumor necrosis rate is sometimes a problem. One reason is insufficient tissue to evaluate the necrosis rate in patients receiving "autograft" reconstruction. Another problem is that not every pathologist follows the standard histologic classification because it is time-consuming.[25] We have attempted to use MRI and nuclear medicine studies as auxiliary tools to estimate the tumor necrosis rate. The conclusion regarding how the results correspond to the pathologic necrosis rate is still pending.

We did not analyze the prognostic factors for the preadolescent patients in our study because of the low number of patients enrolled. Two of the preadolescent patients (patients 7 and 11) with extremely high ALP levels (twice that of normal) and without primary metastasis relapsed quickly after completion of adjuvant chemotherapy, with both showing bony metastasis. This observation is consistent with the fact that a high ALP level is a poor prognostic factor.[26] Whether or not extremely high ALP levels indicate a greater possibility of bony metastasis in preadolescent patients needs more evaluation. In addition, in our experience, a judgment of primary metastasis is sometimes difficult, and the prognosis after relapse remains dismal despite aggressive rescue therapy. For example, patient 8, who showed increased uptake in the left humerus on diagnostic bone scanning, had a negative biopsy result initially. Despite the 100% tumor necrosis rate after neoadjuvant chemotherapy, relapse in the left humerus was found 4 months after completing the entire chemotherapy regimen. Thus, we emphasize that primary metastasis may be vague and the clinical course of patients with suspicious lesions should be highly guarded. The 2 patients (patients 1 and 4) who received autologous PBSCT died of progressive disease and transplantation-related complications quickly, although patient 4 was disease-free at transplantation. As autologous PBSCT is not beneficial,[27] we suggest that it should not be used as rescue therapy for relapsed osteosarcoma. Before the discovery of new effective therapy for relapsed osteosarcoma,[26] early diagnosis and complete resection were considered the most important.

We also found that Chinese traditional therapies, including acupuncture, herbal applications, and massage, were quite commonly used in our patient population (Table 3). These treatments can delay diagnosis or cause micrometastasis during aggressive manipulations. Although we could not collect data for all the patients and analyze the effect on survival, the high

prevalence of traditional therapy deserves investigation on how it may impact osteosarcomas in the general population.

Although this study was a retrospective analysis in a single institute, with relatively small patient numbers, it offers the first report on treating preadolescent Chinese osteosarcoma patients in Taiwan. In conclusion, the general appearance of osteosarcoma and survival in preadolescent patients is not different from those seen in adolescent patients. Multicenter studies with larger patient numbers are warranted to confirm the characteristics of preadolescent osteosarcoma patients and the effect of tumor necrosis rate on survival. Before the results are obtained, we suggest treating these patients according to the same general principles and strategies as those used for adolescent patients.

References

1. Senac MO Jr, Isaacs H, Gwinn JL. Primary lesions of bone in the 1st decade of life: retrospective survey of biopsy results. *Radiology* 1986;160:491–5.
2. Scranton PE Jr, DeCicco FA, Totten RS, Yunis EJ. Prognostic factors in osteosarcoma: a review of 20 years at the University of Pittsburg Health Center hospitals. *Cancer* 1975;36:2179–91.
3. Winkler K, Beron G, Kotz R, Salzer-Kuntschik M, Beck J, Beck W, Brandeis W, et al. Neoadjuvant chemotherapy for osteosarcoma: results of a cooperative German/Austrian study. *J Clin Oncol* 1984;2:617–24.
4. French Bone Tumor Study Group. Age and dose of chemotherapy as major prognostic factors in a trial of adjuvant therapy of osteosarcoma combining two alternating drug combinations and early prophylactic lung irradiation. *Cancer* 1988; 61:1304–11.
5. Bacci G, Longhi A, Bertoni F, Bacchini P, Ruggeri P, Versari M, Picci P. Primary high-grade osteosarcoma: comparison between preadolescent and older patients. *J Pediatr Hematol Oncol* 2005;27:129–34.
6. Cho WH, Lee SY, Song WS, Park JH. Osteosarcoma in preadolescent patients. *J Int Med Res* 2006;34:676–81.
7. Rytting M, Pearson P, Raymond AK, Ayala A, Murray J, Yasko AW, Johnson M, et al. Osteosarcoma in preadolescent patients. *Clin Orthop Relat Res* 2000;373:39–50.
8. Bacci G, Balladelli A, Palmerini E, Alberghini M, Pollastri P, Galletti S, Mercuri M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities in preadolescent patients: the Rizzoli Institute experience. *J Pediatr Hematol Oncol* 2008; 30:908–12.
9. Lockitch G, Halstead AC, Albersheim S, MacCallum C, Quigley G. Age- and sex-specific pediatric reference intervals for biochemistry analyzes as measured on the Ektachem-700 analyzer. *Clin Chem* 1988;34:1622–5.
10. Bacci G, Briccoli A, Ferrari S, Longhi A, Mercuri M, Capanna R, Donati D, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. *Eur J Cancer* 2001;37:2030–9.
11. Chen WM, Chen TH, Huang CK, Chiang CC, Lo WH. Treatment of malignant bone tumours by extracorporeally irradiated autograft-prosthetic composite arthroplasty. *J Bone Joint Surg Br* 2002;84:1156–61.
12. Chen TH, Chen WM, Huang CK. Reconstruction after intercalary resection of malignant bone tumours: comparison between segmental allograft and extracorporeally-irradiated autograft. *J Bone Joint Surg Br* 2005;87:704–9.
13. Huang TL, Chen TH, Chen WY, Chen WM, Liu CL, Lo WH. Allograft arthrodesis of the knee in high-grade osteosarcoma. *J Chin Med Assoc* 2005;68:425–30.
14. Hung GY, Chiou T, Hsieh YL, Yang MH, Chen WY. Intestinal metastasis causing intussusception in a patient treated for osteosarcoma with history of multiple metastases: a case report. *Jpn J Clin Oncol* 2001;31:165–7.
15. Hung MC, Hung GY, Lin PC, Tiu CM, Tien Y.C. Acute pancreatitis associated with ifosfamide. *J Chin Med Assoc* 2007; 70:176–9.
16. Lin MT, Lin KH, Lin DT, Yang RS, Wu CT, Lu MY, Hung IJ, et al. Unstratified chemotherapy for non-metastatic osteosarcoma of the extremities in children. *J Formos Med Assoc* 2003; 102:387–93.
17. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer* 2009;115: 1531–43.
18. Neel MD, Wilkins RM, Rao BN, Kelly CM. Early multicenter experience with a noninvasive expandable prosthesis. *Clin Orthop Relat Res* 2003;415:72–81.
19. Rao BN, Rodriguez-Galindo C. Local control in childhood extremity sarcomas: salvaging limbs and sparing function. *Med Pediatr Oncol* 2003;41:584–7.
20. Lewis IJ, Nooij MA, Whelan J, Sydes MR, Grimer R, Hogendoorn PC, Memon MA, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. *J Natl Cancer Inst* 2007;99:112–28.
21. Eselgrim M, Grunert H, Kühne T, Zoubek A, Kevric M, Bürger H, Jürgens H, et al. Dose intensity of chemotherapy for osteosarcoma and outcome in the Cooperative Osteosarcoma Study Group (COSS) trials. *Pediatr Blood Cancer* 2006;47: 42–50.
22. Bacci G, Mercuri M, Longhi A, Ferrari S, Bertoni F, Versari M, Picci P. Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. *Eur J Cancer* 2005;41:2079–85.
23. Sami SH, Rafati AH, Hodjat P. Tissue necrosis after chemotherapy in osteosarcoma as the important prognostic factor. *Saudi Med J* 2008;29:1124–9.
24. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. *Cancer* 1979;43: 2163–77.
25. Bramer JA, Abudu AA, Tillman RM, Carter SR, Sumathi VP, Grimer RJ. Pre- and post-chemotherapy alkaline phosphatase levels as prognostic indicators in adults with localized osteosarcoma. *Eur J Cancer* 2005;41:2846–52.
26. Sauerbrey A, Bielack S, Kempf-Bielack B, Zoubek A, Paulussen M, Zintl F. High-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (ASCT) as salvage therapy for relapsed osteosarcoma. *Bone Marrow Transplant* 2001;27:933–7.
27. Chou AJ, Geller DS, Gorlick R. Therapy for osteosarcoma: where do we go from here? *Paediatr Drugs* 2008;10:315–27.