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Improvement in High-Grade Osteosarcoma Survival

Results from 202 Patients Treated at a Single Institution in Taiwan

Giun-Yi Hung, MD, Hsiu-Ju Yen, MD, Chueh-Chuan Yen, MD, PhD, Po-Kuei Wu, MD, Cheng-Fong Chen, MD, Paul C-H Chen, MD, Hung-Ta H. Wu, MD, Hong-Jen Chiou, MD, and Wei-Ming Chen, MD

Abstract: The aim of this study was to compare survival before and after 2004 and define the prognostic factors for high-grade osteosarcomas beyond those of typical young patients with localized extremity disease.

Few studies have reported the long-term treatment outcomes of high-grade osteosarcoma in Taiwan.

A total of 202 patients with primary high-grade osteosarcoma who received primary chemotherapy at Taipei Veterans General Hospital between January 1995 and December 2011 were retrospectively evaluated and compared by period (1995–2003 vs 2004–2011). Patients of all ages and tumor sites and those following or not following controlled protocols were included in analysis of demographic, tumor-related, and treatment-related variables and survival.

Overall survival and progression-free survival at 5 years were, respectively, 67.7% and 48% for all patients (n = 202), 77.3% and 57.1% for patients without metastasis (n = 157), and 33.9% and 14.8% for patients with metastasis (n = 45). The survival rates of patients treated after 2004 were significantly higher (by 13%–16%) compared with those of patients treated before 2004, with an accompanying 30% increase in histological good response rate ($P = .002$). Factors significantly contributing to inferior survival in univariate and multivariate analyses were diagnosis before 2004, metastasis at diagnosis, and being a noncandidate for a controlled treatment protocol.

By comparison with the regimens used at our institution before 2004, the current results support the effectiveness of the post-2004 regimens, which consisted of substantially reduced cycles of high-dose methotrexate and a higher dosage of ifosfamide per cycle, cisplatin, and doxorubicin, for treating high-grade osteosarcoma in Asian patients.

Editor: Goran Augustin.
Received: August 31, 2015; revised and accepted: March 24, 2016.
From the Department of Pediatrics, Division of Pediatric Hematology and Oncology (G-YH, H-JY); Department of Orthopedics, Therapeutical and Research Center of Musculoskeletal Tumor, Taipei Veterans General Hospital (G-YH, H-JY, C-CY, P-KW, C-FC, PC-HC, H-THW, H-JC, W-MC); School of Medicine, National Yang-Ming University (G-YH, H-JY, C-CY, C-FC, PC-HC, H-THW, H-JC, W-MC); Department of Life Science, National Taiwan Normal University (G-YH, H-JY); Department of Oncology, Division of Medical Oncology, Taipei Veterans General Hospital (C-CY); Institute of Clinical Medicine, National Yang-Ming University (P-KW); Department of Orthopedics (P-KW, C-FC); Department of Pathology (PC-HC); Department of Radiology (H-THW, H-JC); National Defense Medical Center (H-JC); and Rehabilitation and Technical Aid Center, Taipei Veterans General Hospital, Taipei, Taiwan (W-MC).

Correspondence: Chueh-Chuan Yen, Department of Oncology, Division of Medical Oncology, Taipei Veterans General Hospital, No. 201, Sec 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C
(e-mail: ccyen@vghtpe.gov.tw).
The authors report no conflicts of interest.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003420

(*Medicine* 95(15):e3420)

Abbreviations: AYA = adolescents and young adults, Epi = epirubicin, GR = pathological good responders, Ifo = ifosfamide, M = high-dose methotrexate, NHI = National Health Insurance, OS = overall survival, P = cisplatin, PFS = progression-free survival, PR = pathological poor responders, SMNs = secondary malignant neoplasms, TPOG = Taiwan Pediatric Oncology Group, TVGH = Taipei Veterans General Hospital.

INTRODUCTION

Osteosarcoma is rare and accounts for <0.2% of all cancers, with only approximately 60 cases diagnosed annually in Taiwan.[1] It is more common in children and adolescents and comprises 4% of cancers in people older than 20 years.[1,2] Because of the rarity of the disease, relatively few reports regarding the treatment outcome of controlled protocols for osteosarcoma are available in Taiwan. To date, only 2 studies have investigated the outcomes of chemotherapy for pediatric osteosarcoma of the extremities.[3,4] One study was conducted by the Taiwan Pediatric Oncology Group (TPOG) in a multicenter setting; this large series reported 7-year overall survival (OS) and event-free survival of 67.6% and 51.6%, respectively, for the TPOG OS-94 protocol.[3] The other study was a single-institution report from the authors' hospital, Taipei Veterans General Hospital (TVGH), which showed that the 5-year OS and progression-free survival (PFS) rates were 77% and 70%, respectively, for the TVGH OGS M2, TVGH OGS 001, and TVGH OGS 2008 protocols.[4] These limited results of osteosarcoma survival after chemotherapy are similar to those obtained in Japan and Western countries.[5–8] The aim of the present study was to evaluate the overall outcomes of a wide range of osteosarcomas, extending beyond those of typical young patients with localized extremity disease. Moreover, in consideration of the substantial change in chemotherapy regimens after 2004, the survival rates of patients diagnosed before and after 2004 were compared.

PATIENTS AND METHODS

Patients

A total of 347 patients diagnosed with osteosarcoma who visited TVGH for treatment between January 1995 and December 2011 were retrospectively evaluated for eligibility (Figure 1). Of these patients, we excluded 145, of whom 99 underwent surgery or consultation only, 26 (17.9%) had secondary osteosarcoma or double cancer, 11 (7.6%) had low-grade osteosarcoma, and 9 (6.2%) were lost to follow-up. The remaining 202 patients with primary high-grade osteosarcoma who had received primary treatment at our institution were

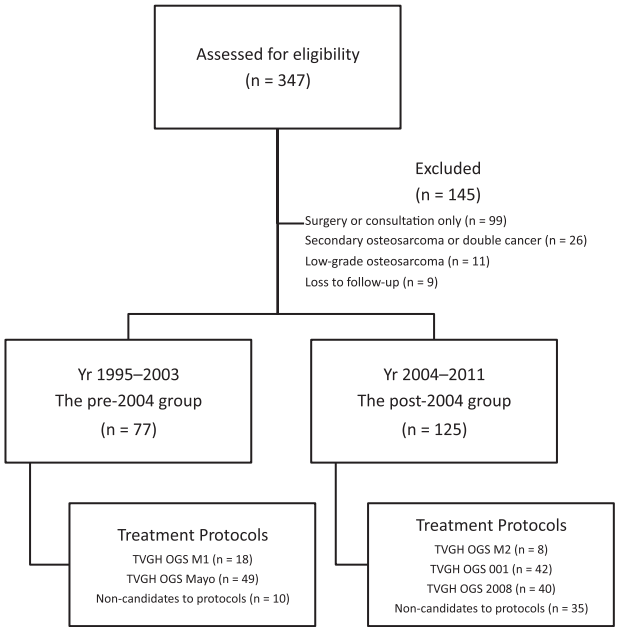

FIGURE 1. Flow diagram of patient recruitment for the final analyses. Yr = year.

included in this analysis. Of these patients, 77 (38.1%) were diagnosed during 1995 to 2003 (defined as the pre-2004 group) and 125 (61.9%) during 2004 to 2011 (defined as the post-2004 group). In addition, 157 patients (77.7%) were enrolled in controlled protocols (ie, protocols consisting of preoperative chemotherapy, tumor excision, and postoperative chemotherapy), and 45 (22.3%) were not candidates for any protocol (ie, they underwent chemotherapy, radiotherapy, or surgery before being referred to our institution). The survival rate but not the surgical outcome was evaluated for 2 patients because one had undergone surgery elsewhere and had only received postoperative chemotherapy at our institution, and the other patient did not undergo surgery because of diffuse disease. This study followed the guidelines of TVGH and was approved before initiation by the Tumor Board of Therapeutical and Research Center of Musculoskeletal Tumor of TVGH.

Treatment

As shown in Figure 1, 157 patients were treated according to the protocols active at the time of enrollment, including TVGH OGS M1 (n = 18), TVGH OGS Mayo (n = 49), TVGH OGS M2 (n = 8), TVGH OGS 001 (n = 42), and TVGH OGS 2008 (n = 40). The details of these chemotherapeutic regimens are provided in Table 1. Informed consent for chemotherapy was obtained from every patient or the patient's legal guardian before the initiation of chemotherapy. In addition, the Cancer Treatment Quality Monitoring Board had approved the TVGH OGS 2008 protocol. All these protocols included preoperative and postoperative chemotherapy, and these regimens have previously been partially or completely described.[4,9,10] Before 2004, most patients (n = 49) received the TVGH OGS Mayo protocol, a primary treatment consisting of high-dose methotrexate (M), epirubicin (Epi), cisplatin (P), and ifosfamide (Ifo). Other patients (n = 18) received the TVGH OGS M1 protocol, which consisted of the same 4 drugs (M–Epi–P–Ifo) in addition to etoposide. After 2004, patients received different protocols (ie, the TVGH OGS 001, 2008, and M2 protocols), which consisted of M–P–Ifo and doxorubicin (A), that is, M–A–P–Ifo regimens. In addition, postoperative chemotherapy was stratified by the histologic response to the TVGH OGS 001 and 2008 protocols (Table 1). In these 2 protocols, pathological good responders (GRs; ie, those with a tumor necrosis rate $\geq$90%) received 8 cycles of postoperative chemotherapy, whereas the pathological poor responders (PRs; ie, those with a tumor necrosis rate <90%) received 12 cycles of postoperative chemotherapy.

Follow-Up

Routine follow-up consisted of radiographic assessments (including radiography, limb ultrasonography, and magnetic resonance imaging of the primary site), plain chest radiography, and chest computed tomography. A whole-body bone scan was performed to identify distant bone metastases. After completion of chemotherapy, these assessments were conducted every 3 months during the first 2 years, every 6 months for the subsequent 3 years, and every 12 months thereafter.

Statistical Analysis

Patient characteristics, tumor features, and treatment-related variables were compared between patients with osteosarcoma diagnoses made before and after 2004 by using the χ^2 test or the Fisher exact test. OS was defined as the time from the date of diagnosis to the date of death or the final follow-up. PFS was defined as the time from the date of diagnosis to the date of treatment failure (ie, progression, relapse, death, or the development of a second malignancy) or until the final follow-up for all patients without the described events. The OS and PFS curves were generated using the Kaplan–Meier method and compared using the log-rank test. The parameters evaluated in the univariate analysis were used as explanatory variables in the Cox regression models of OS and PFS and the final multivariate models. Two-sided $P < 0.05$ was defined as statistically significant. S-PLUS 2000 software was used for data analysis. The data of patients used in these analyses were last updated on July 14, 2014.

RESULTS

Patients

The patient characteristics, tumor features, and treatment-related variables of the 202 patients with primary high-grade osteosarcoma at all sites were analyzed and are presented by period (1995-2003 vs 2004-2011) in Table 2. Overall, the male:female ratio was 1.7:1, and the mean age at diagnosis was 18.1 ± 11.2 years (median, 15.4 years; range, 3.8–66.4). Patients aged <18, 18 to 39, and $\geq$40 years accounted for 72.3%, 19.8%, and 7.9% of all patients, respectively. The most common tumor site was the extremities (n = 193; 95.5%). Seven (3.5%) of these tumors originated in the pelvis, and only 2 (1%) were located at other sites. Forty-five (22.3%) patients had metastatic disease at diagnosis, of whom 26 (57.8%) had pulmonary metastases, 13 (28.9%) had bone metastases, 5 (11.1%) had both pulmonary and bone metastases, and 1 (2.2%) had simultaneous metastases in the bone, lung, and liver. Four patients developed secondary malignant neoplasms (SMNs; acute myeloid leukemia in 2, acute lymphoblastic leukemia in 1, and Langerhans cell histiocytosis in 1), with an overall incidence of 2% for SMN. Comparison of the characteristics of the pre- and post-2004 groups revealed that

TABLE 1. The Chemotherapeutic Regimens Used for 157 Patients With High-grade Osteosarcoma Treated at TVGH During 1995–2011

Study Period	Number of Patients	Metastastic or Unresectable Disease	Preoperative Chemotherapy (Dose) × Cycles	Postoperative Chemotherapy (Dose) × Cycles	Cumulative Doses of Chemotherapeutic Drugs						Total Duration of Chemotherapy, wk
					M, g/m^2	A, mg/m^2	P, mg/m^2	Ifo, g/m^2	Epi, mg/m^2	VP, mg/m^2	
TVGH OGS M1 1995–2003	18	Allowed	M (12) × 6 Epi (100) + P (120) × 1 Ifo (12) + VP (300) × 2	M (12) × 8 Epi (100) + P (120) × 2 Epi (75)+P (150) × 2 Ifo (12) + VP (300) × 3	168		660	60	450	1500	43
TVGH OGS Mayo 1995–2003	49	Allowed	M (12) × 6 Ifo (9) + Epi (75) × 2 Epi (75) + P (120) × 1	M (12) × 10 Ifo (9) + Epi (75) × 2 Epi (75) + P (120) × 1 Ifo (9) × 2 P (120) × 1	192		360	54	450		41
TVGH OGS M2 2004–2014	8	Allowed	A (90) + P (120) × 1 A (75) + P (150) × 1 Ifo (15) × 2	M (12) × 4 A (90) + P (120) × 2 A (75) + P (150) × 2 Ifo (15) × 4	48	495	810	90			42
TVGH OGS 001* 2004–2007	42	No	M (12) × 2 A (75) + P (120) × 2 Ifo (15) × 2	GR: M (12) × 2 A (90) × 2 P (150) × 2 Ifo (15) × 2	48	330	540	60			32
				PR: M (12) × 3 A (90) × 3 P (150) × 3 Ifo (15) × 3	60	420	690	75			42
TVGH OGS 2008* 2008–2011	40	No	M (12) × 2 A (75) + P (120) × 2 Ifo (15) × 1	GR: M (12) × 2 A (90) × 2 P (150) × 2 Ifo (15) × 2	48	330	540	45			29
				PR: M (12) × 3 A (90) × 3 P (150) × 3 Ifo (15) × 3	60	420	690	60			39

A = adriamycin, Epi = epirubicin, GR = pathological good responder, Ifo = ifosfamide, M = methotrexate, P = cisplatin, PR = pathological poor responder, TVGH = Taipei Veterans General Hospital, VP = etoposide.
*The protocols were stratified postoperatively according to histologic response (GR, tumor necrosis ≥90%; PR, tumor necrosis <90%).

TABLE 2. Patient Characteristics, Tumor Features, and Treatment-related Variables of High-grade Osteosarcomas (n = 202) Treated at TVGH According to Study Period (1995–2003 vs 2004–2011)

			Study Period				
	All		1995–2003		2004–2011		
	n = 202		n = 77		n = 125		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Sex							0.77
Male	126	62.4	49	63.6	77	61.6	
Female	76	37.6	28	36.4	48	38.4	
Age, y							0.03
<18	146	72.3	63	81.8	83	66.4	
18–39	40	19.8	12	15.6	28	22.4	
≥40	16	7.9	2	2.6	14	11.2	
Site							
Extremity	193	95.5	75	97.4	118	94.4	
Pelvis	7	3.5	2	2.6	5	4	
Others	2	1			2	1.6	
Metastasis							0.52
Yes	45	22.3	19	24.7	26	20.8	
No	157	77.7	58	75.3	99	79.2	
Candidate to protocols*							0.15
Yes	157	77.7	64	83.1	93	74.4	
No	45	22.3	13	16.9	32	25.6	
Type of surgery (n = 200)							0.03
Amputation	12	6	8	10.5	4	3.2	
Limb-salvage	188	94	68	89.5	120	96.8	
Surgical margins (n = 170)							0.007
Negative	164	96.5	51	91.1	113	99.1	
Positive	6	3.5	5	8.9	1	0.9	
Histological response (n = 139)†							0.002
GR	93	66.9	14	43.8	79	73.8	
PR	46	33.1	18	56.3	28	26.2	

GR = pathological good responders, PR = pathological poor responders, TVGH = Taipei Veterans General Hospital.

*A candidate to protocols indicates an eligible patient for any controlled protocols (ie, protocols which consisted of preoperative chemotherapy, tumor excision and postoperative chemotherapy), noncandidate to protocols indicates a patient having prior chemotherapy or radiotherapy, or surgery before being referred to our institution.

†GR, tumor necrosis ≥90%; PR, tumor necrosis <90%.

they differed significantly only in age. Of the patients older than 18 years, significantly more were diagnosed after 2004 ($P = 0.03$). A nonsignificant increase in the proportion of patients who were not candidates for protocols was noted after 2004 ($P = 0.15$).

Surgical Outcome

In 200 assessable patients, 188 (94%) underwent limb-salvage surgery, with the remaining 12 (6%) undergoing amputation (Table 2). The reasons for amputation were either the large size or rapid progression of the tumor after initial diagnosis. Positive margins after limb-salvage surgery were found in 6 (3.5%) of the 170 assessable patients. Among 139 assessable patients, GR (n = 93) accounted for 66.9%. A comparison of the surgical results of the pre- and post-2004 groups revealed that the number of patients undergoing limb-salvage surgery significantly increased (89.5%–96.8%, $P = 0.03$). By contrast, the number of patients undergoing amputation decreased (10.5%–3.2%). Moreover, the number of patients with negative surgical margins increased significantly (91.1%–99.1%, $P = 0.007$). Furthermore, the GR rate increased significantly by 30% (43.8%–73.8%, $P = 0.002$) for the post-2004 group.

Survival

Table 3 presents the relationship, determined through univariate analysis, of the examining factors with the survival rates of the 202 patients. The median follow-up time was 8 years (range, 2.7–19.7 years). Seventy-four of the 202 patients died from the disease; the cause of death was disease relapse or progression for 71 patients (95.9%), with 1 patient (1.4%) dying each from secondary neoplasia (acute myeloid leukemia), infection (septic shock), and drug-related pneumonitis (owing to everolimus). The overall toxicity-related death rate was 1% (2/202 patients). The estimated 5-year OS and PFS rates of the patients without metastasis were 77.3% and 57.1%, respectively, and those of the patients with metastasis were 33.9% and 14.8%, respectively.

TABLE 3. Univariate Analysis of OS and PFS Based on Kaplan-Meier Estimates and Log-rank Tests for Patients With High-grade Osteosarcoma (n = 202) Treated at TVGH From 1995 to 2011

		5-year OS			5-year PFS		
Factors	**n**	**%**	**SE (%)**	***P***	**%**	**SE (%)**	***P***
All patients	202	67.7	3.4		48	3.6	
Period				0.04			0.03
1995–2003	77	59.7	5.6		38.3	5.6	
2004–2011	125	72.6	4.2		54.0	4.6	
Sex				0.59			0.45
Male	126	65.3	4.4		46.0	4.6	
Female	76	71.8	5.2		51.3	5.7	
Age, y				0.02			0.15
<18	146	69.9	3.9		52.6	4.2	
18–39	40	68.8	7.5		35.0	7.5	
≥40	16	43.8	12.4		41.7	12.7	
Site							
Extremity	193	69.3	3.4		48.9	3.7	
Pelvis	2						
Others	7						
Metastasis				<0.001			<0.001
Yes	45	33.9	7.3		14.8	5.8	
No	157	77.3	3.5		57.1	4.0	
Candidate to protocols*				<0.001			<0.001
Yes	157	72.8	3.6		55.1	4.0	
No	45	50.1	7.6		22.7	6.4	
Type of surgery (n = 200)				0.64			0.27
Amputation	12	58.3	14.2		41.7	14.2	
Limb-salvage	188	68.4	3.5		48.3	3.7	
Surgical margins (n = 170)				<0.001			<0.001
Negative	164	73.8	3.5		55.0	4.0	
Positive	6	16.6	15.2		0	–	
Histologic response (n = 139)†				<0.001			<0.001
GR	93	82.8	4.1		68.2	4.9	
PR	46	45.7	7.6		18.5	5.9	

GR = pathological good responders, OS = overall survival, PFS = progression-free survival, PR = pathological poor responders, TVGH = Taipei Veterans General Hospital.

*A candidate to protocols indicates an eligible patient for any controlled protocols (ie, protocols which consisted of preoperative chemotherapy, tumor excision, and postoperative chemotherapy), noncandidate to protocols indicates a patient having previous chemotherapy or radiotherapy, or surgery before being referred to our institution.

†GR, tumor necrosis ≥90%; PR, tumor necrosis <90%.

Disease progression was observed in 104 patients (51.5%). The median time to progression was 1.4 years (range, 18 days-7.5 years). The lungs were the most common sites of progression. Of the 104 patients, 37 (35.6%) had primary metastases, and a more rapid progression was observed in these patients than in those without primary metastases (mean, 13.5 vs 22.7 months, $P = 0.001$). Thirty-five patients with disease progression (33.7%) were still alive at the time of this study; however, only 5 (14.3%) of these patients had primary metastases.

Figure 2A and B shows the long-term OS and PFS curves of all patients (n = 202) and those of patients in the pre-2004 (n = 77) and post-2004 groups (n = 125). For all patients, the estimated 5- and 10-year OS rates were 67.7% and 59%, respectively, and the 5- and 10-year PFS rates were 48% and 47.1%, respectively. For the patients in the pre-2004 group, the 5- and 10-year OS were 59.7% and 50.6%, respectively, and the 5- and 10-year PFS were both 38.3%. For the patients in the post-2004 group, the 5- and 10-year OS rates were 72.6% and 66.7%, respectively, and the 5- and 10-year PFS rates were 54% and 51.7%, respectively. The OS ($P = .04$) and PFS ($P = .03$) rates of the post-2004 group were significantly higher (13%–16%) than those of the pre-2004 group. In addition, Figure 2C and D present the long-term OS and PFS curves of all patients with tumors in the extremities (n = 193) and of these patients in the pre-2004 (n = 75) and post-2004 groups (n = 118). The results were similar for all patients with primary tumors at all sites, with the post-2004 group exhibiting a significant improvement of 13% to 16% in OS ($P = .04$) and PFS ($P = .03$).

Prognostic Factors

Tables 3 and 4 show the relationships between multiple factors and survival obtained through univariate analysis and multivariate Cox regression models, respectively. In the univariate analysis, age was a significant factor associated with OS

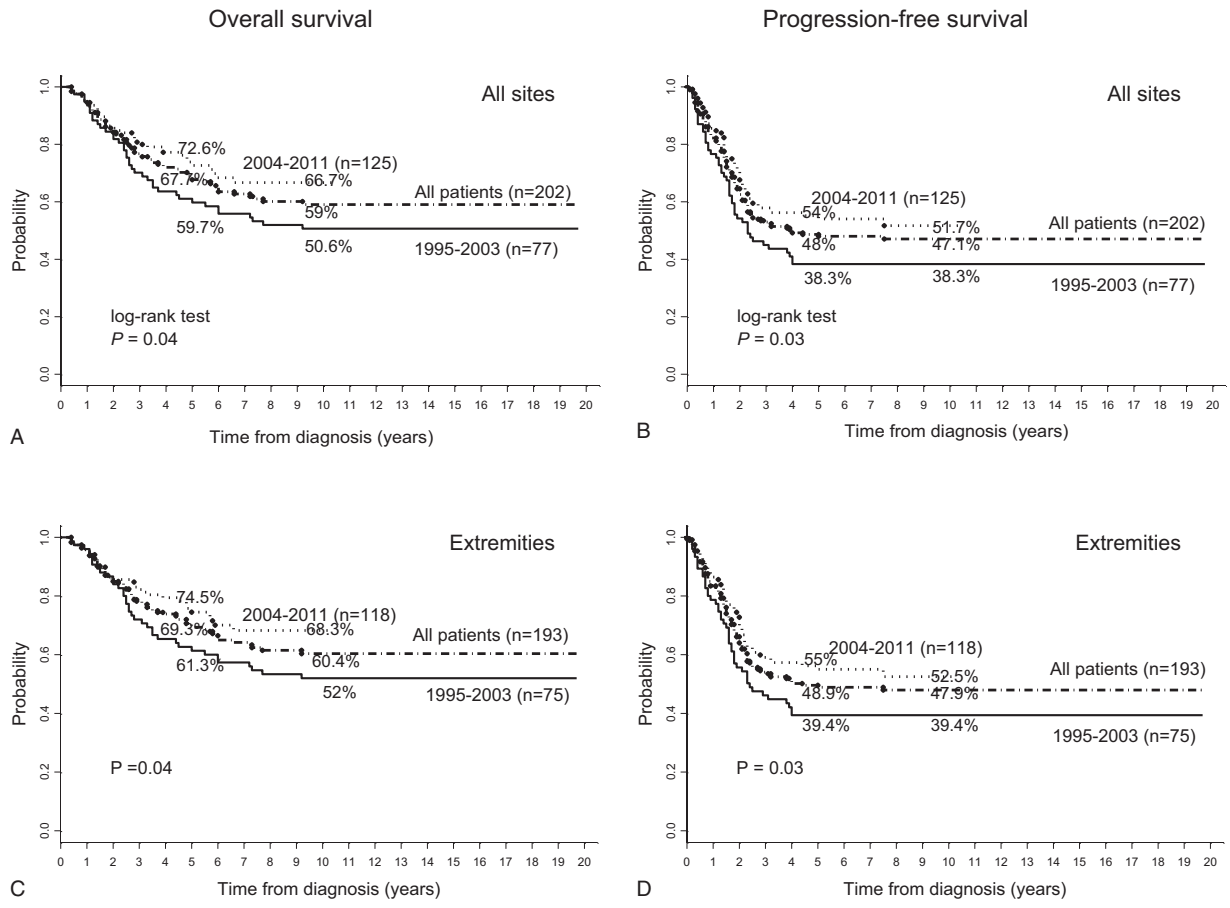

FIGURE 2. Overall survival and progression-free survival curves of patients with high-grade osteosarcoma by study period (1995–2003, 2004–2011, and overall). (A, B) All primary sites; (C, D) extremities as the primary site.

(Table 3, $P = 0.02$), and the correlation between young age and GR rate was significant (73.5% and 51.9% for ages <18 and 18–39 years, respectively, $P = 0.03$). However, age was not significantly correlated with OS in the multivariate analysis ($P = 0.33$, Table 4). Moreover, age was not significantly correlated with PFS in the univariate or multivariate analyses ($P = 0.15$, Tables 3 and 4). Furthermore, the mean time to progression did not differ significantly between patients aged <18 and 18 to 39 years (1.5 and 1.8 years, respectively, $P = 0.46$).

In the univariate analysis, surgery type and sex were not significantly correlated with survival. The variables that were negatively correlated with OS and PFS were treatment period (1995–2003), metastasis at diagnosis, positive surgical margins, PR, and being a noncandidate for a controlled treatment protocol (Table 3). In the multivariate analysis, the factors significantly contributing to inferior OS and PFS were the treatment period (1995–2003), metastasis at diagnosis, and being a noncandidate for a treatment protocol, with relative risks of 1.82, 4.66, and 2.39 for OS and 1.6, 3.64, and 2.37 for PFS, respectively (Table 4). The long-term OS and PFS curves are stratified by the prognostic factors of metastasis at diagnosis (nonmetastasis vs metastasis, $P < 0.001$) in Figure 3A and B and by protocol eligibility (candidate vs noncandidate, $P < 0.001$) in Figure 3C and D.

DISCUSSION

Comparison of OS and PFS results of all the selected osteosarcoma patients treated during 1995 to 2003 and 2004 to 2011 revealed a significant improvement of 13% to 16% after 2004 (Figure 2). Moreover, the GR rate increased significantly by 30% (43.8%–73.8%, $P = 0.002$; Table 2) for this post-2004 group. Univariate and multivariate analyses revealed that the variables that significantly contributed to inferior OS and PFS were treatment period (1995–2003), metastasis at diagnosis, and being a noncandidate for a treatment protocol.

One of the most crucial factors contributing to the increase in survival of the post-2004 group was improvement in the treatment protocols. Compared with the chemotherapeutic regimens used before 2004 (ie, TVGH OGS Mayo and M1 protocols, Table 1), those used after 2004 (ie, TVGH OGS M2, 001, and 2008 protocols; M–A–P–Ifo regimen; Table 1) consisted of substantially reduced cycles of high-dose methotrexate, used more cycles and a higher dosage of cisplatin per cycle, used a higher dosage of Ifo per cycle (15 g/m^2/cycle compared with 9–12 g/m^2/cycle before 2004), used adriamycin instead of epirubicin, and omitted etoposide. A previous study from our institution analyzed the outcomes of pediatric osteosarcoma of the extremities and reported that these new protocols increased the GR rate by 30% and survival by 20%.[4] Similarly, the present study found significant GR and survival rate

TABLE 4. Multivariate Analysis of Variables and Survivals in Patients With High-grade Osteosarcoma (n = 202) Treated at TVGH From 1995 to 2011 by Cox Regression Models

	Overall Survival			Progression-free Survival		
Variables	**RR**	**(95% CI)**	***P***	**RR**	**(95% CI)**	***P***
Study period			0.017			0.02
1995–2003 vs 2004-2011	1.82	(1.11–2.98)		1.6	(1.07–2.39)	
Sex			0.69			1
Male vs female	1.11	(0.68–1.80)		1	(0.67–1.50)	
Age. y			0.33			0.15
18–39 vs <18	1.31	(0.76–2.27)		1.38	(0.89–2.14)	
Metastasis			<0.001			<0.001
Yes vs no	4.66	(2.90–7.50)		3.64	(2.40–5.52)	
Candidate to protocols*			0.001			<0.001
No vs yes	2.39	(1.41–4.03)		2.37	(1.53–3.66)	

CI = confidence interval, RR = relative risk, TVGH = Taipei Veterans General Hospital.
*A candidate to protocols indicates an eligible patient for any controlled protocols (ie, protocols that consisted of preoperative chemotherapy, tumor excision, and postoperative chemotherapy), noncandidate to protocols indicates a patient having previous chemotherapy or radiotherapy, or surgery before being referred to our institution.

improvements of 30% and 13% to 16%, respectively, in patients of all ages and primary sites. Evidently, patients treated with these new chemotherapeutic regimens (M–A–P–Ifo regimen) after 2004 exhibited an improved histologic response, leading to a higher likelihood of survival.

In most parts of Asia, where viral hepatitis B and C infection is endemic, the hepatitis B surface antigen seropositive rate in the general population is approximately 5% to 20%.[11,12] Therefore, the potential risk of a hepatitis flare-up among viral hepatitis carriers during chemotherapy is a serious concern. Modifying osteosarcoma treatment protocols adopted from Western countries and adjusting these regimens are urgent tasks for healthcare providers in Asia to reduce hepatotoxicity. Among the chemotherapeutic drugs most commonly used for treating high-grade osteosarcoma, the >3 drug (M–A–P [Ifo]) regimens were found in a meta-analysis to be the most efficacious for patients with localized disease.[13] The study also reported no significant difference in outcome analysis between M–A–P and M–A–P–Ifo (or plus etoposide) regimens. High-dose methotrexate is the most hepatotoxic agent among these drugs. A study in China showed that methotrexate-free regimens (A-P-Ifo regimen) resulted in survival outcomes comparable with those of methotrexate-containing regimens but with fewer adverse reactions.[14] Another study reported the efficacy of M–A–P–Ifo regimens in 185 Chinese patients with osteosarcoma.[15] Two Japanese studies demonstrated the efficacy of adding high-dose Ifo (15–16 g/m^2) to the standard 3-drug (M–A–P) chemotherapy regimens, with one of the studies finding 5-year OS and event-free survival rates of up to 98% and 83%, respectively, for nonmetastatic extremity disease.[6,16] Our previous experience of treating nonmetastatic pediatric osteosarcoma of the extremities with M–A–P–Ifo regimens also showed similar results, finding 5-year OS and PFS rates of 90.4% and 83.3%, respectively.[4] The results of our previous study of pediatric osteosarcomas and those of the present study, along with the results of the aforementioned studies performed in other East Asian countries, have demonstrated survival outcomes similar to those obtained from contemporaneous Western studies.[5,17,18] Thus, these results strongly support the feasibility of using M–A–P–Ifo regimens with substantially reduced cycles of high-dose methotrexate, but higher doses of Ifo per cycle for Asian patients. Further research into less hepatotoxic regimens for osteosarcoma treatment in Asia is required. Different drug susceptibility might exist between Asians and patients with different ethnic backgrounds. We suggest that randomized controlled trials comparing the efficacy of regimens with or without high-dose methotrexate (eg, M–A–P–Ifo vs A–P–Ifo regimens) be performed using Asian patients.

The present study revealed that adolescents and young adults (AYAs, aged 18–39 years) had a 5-year OS rate similar to that of children (aged <18 years, 68.8% vs 69.9%, Table 3); however, the 5-year PFS rate was decreased, but nonsignificantly, by 17% (35.0% vs 52.6%, $P = 0.15$). Moreover, the GR rate significantly decreased by 21.6% ($P = 0.03$) for AYA compared with children. Our results are consistent with those of a previous study by the Children's Oncology Group, which reported inferior event-free survival attributed to an increased relapse rate in AYA patients compared with that in children.[5] Moreover, evidence from other studies, including a meta-analysis, indicated that children had higher rates of chemotherapy-induced hematological toxicity and higher tumor necrosis than did adults, suggesting the existence of fundamental differences in the responses to chemotherapy between children and adults.[19,20] The results of our analysis are consistent with those of these previous reports, which have suggested that age-specific tumor biology and/or drug pharmacodynamics/pharmacokinetics result in different tumor histologic responses. Because the response to chemotherapy is an independent prognostic factor for high-grade osteosarcoma,[21,22] additional pharmacodynamics/pharmacokinetics studies are required to investigate the correlation of chemotherapy dosage with histologic response according to patient age to determine the dosage crucial to improving the GR rate. Furthermore, future studies should contribute to the development of age-stratified chemotherapy protocols.

The present study showed that patients who were not candidates for protocols had significantly inferior 5- and 10-

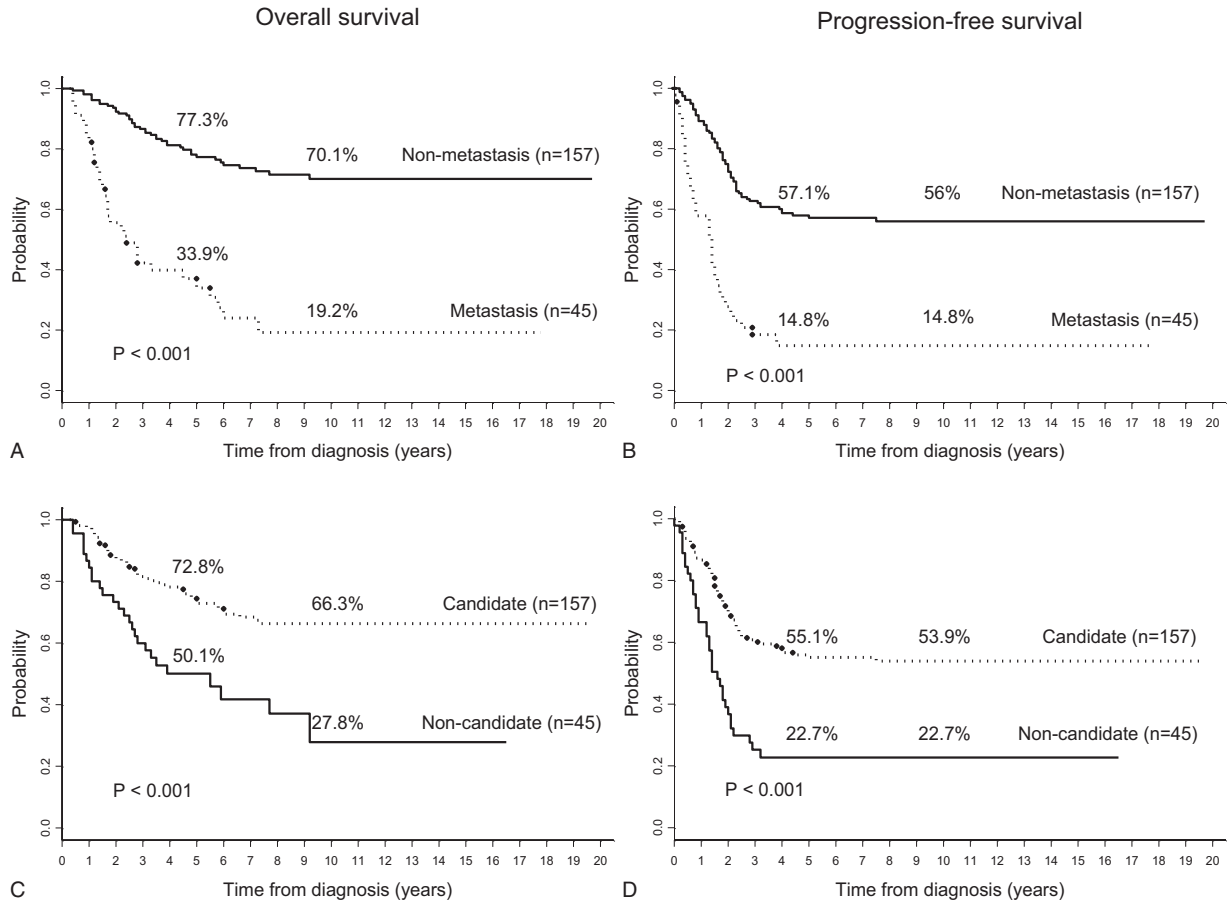

FIGURE 3. Prognostic factors identified using overall survival and progression-free survival curves of patients with high-grade osteosarcoma (n = 202) generated using the Kaplan–Meier method. (A, B) Nonmetastasis vs metastasis at diagnosis; (C, D) candidate vs noncandidate to protocols.

year OS and PFS rates compared with patientswho were candidates (Figure 3C and D). However, attention has not been paid to the underlying causes contributing to the significantly inferior survival rate among these patients. Most previous osteosarcoma studies have evaluated the outcome of the treatment protocol, but excluded patients who underwent previous chemotherapy or surgery.[4–6,8,9,21,23] Thus, the outcome of this group of patients is largely unknown. Most patients with osteosarcomas treated at our institution[1,4,24,25] were referred from other hospitals, and approximately 20% of these patients were either referred for surgical resection of the primary tumor after neoadjuvant chemotherapy or had never received chemotherapy but had undergone previous unplanned surgery before being diagnosed with osteosarcoma. Such patients are ineligible to participate in any study intended to evaluate the treatment outcome of each protocol because of difficulties in evaluating the possible impact of previous treatment on survival. In fact, the most common factors associated with unplanned surgery before diagnosis of osteosarcoma are related to pathological fracture or misdiagnosis,[26–28] and these factors often result in inadequate surgical margins. Tumor bleeding and contamination during surgery can result in increased local recurrence, enhanced tumor cell migration, and distant metastasis, leading to poorer outcomes.[9] In addition, some patients who had received preoperative chemotherapy before being transferred to our institution for definitive surgery decided to receive subsequent postoperative chemotherapy at our institution, resulting in unavoidable adjustment/interruption in their protocols. However, our observations are consistent with those of previous reports,[29] suggesting that artificially interrupted treatment protocols might negatively influence the treatment outcome. Clinicians, patients, and patients' families should be aware of these facts and try to avoid unplanned surgery or otherwise interrupt the treatment protocol as little as possible during osteosarcoma treatment.

Currently, up to 99% of residents of Taiwan are covered by the National Health Insurance (NHI) program.[30] A single-institution study reported that the survival of patients with osteosarcoma improved significantly following the launch of the NHI program in 1995.[31] Although the NHI program benefits most patients, it has some disadvantages. For example, physicians may delay examinations that are more costly (eg, magnetic resonance imaging) because of concerns that insurance claims might be rejected by the NHI administration; consequently, bone tumor diagnoses may be delayed. According to our clinical experience, we suggest that physicians treating patients with osteosarcoma pay more attention to possible unsuspected adjustments when considering the cost of diagnostic imaging techniques, and to the possibility of increased misdiagnosis or delayed diagnosis under the NHI program.

This study has the following limitations. First, the use of a retrospective design covering a long study period may have led to bias caused by improvement in diagnostic technology, surgical techniques, teamwork, and supportive care, and this bias might have influenced the survival estimates. Second, possible factors influencing the statistical power of the results included the recruitment of patients other than typical young patients with localized extremity disease and the inclusion of patients who had received treatments before being referred to our hospital. In addition, only 84% of the 202 patients had surgical margins proven by pathologic evaluation (Table 2). Furthermore, 68.8% of the 202 patients were evaluated according to histologic response (Table 2); the other patients were not evaluated according to histologic response mainly because of the use of autografts after extracorporeal irradiation for limb-salvage surgery.[24,25] These factors have led to an increase in missing data and might have reduced the statistical power for risk factors testing. In addition, potential bias associated with variations in patient age during different periods (patients diagnosed after 2004 were significantly older; Table 2) might have confounded the survival estimates.

In conclusion, this study demonstrated the long-term outcome of high-grade osteosarcoma over 17 years at our institution in patients of all ages and tumor sites. This is the first study of its type in Taiwan to utilize such a large patient cohort and long follow-up period. The patients in this study were considerably heterogeneous but represented patients with osteosarcomas encountered in daily clinical practice. The key factor contributing to the 13% to 16% survival improvement in the patients treated after 2004 was the change to M–A–P–Ifo regimens; this result was supported by the GR rate significantly increasing by 30% after 2004. The results of this study elucidate the long-term outcomes of M–A–P–Ifo regimen use in Asian patients, and indicate that future clinical trials should explore less hepatotoxic regimens for high-grade osteosarcoma in viral hepatitis endemic regions such as Taiwan. Age-specific differences in the GR rate suggest that chemotherapy pharmacodynamics and pharmacokinetics, or tumor biology differ with age. Thus, the development of age-stratified chemotherapy protocols is required to improve the histologic response of neglected AYA patients. Compared with patients who were candidates for a treatment protocol, those who were not had significantly lower 5- and 10-year survival rates. The long-term impact of the nonrecruitment of patients with previous treatment on the survival outcome of these patients might have been underestimated by both physicians and patients.

ACKNOWLEDGMENTS

We thank Wan-Hui Chang for her contribution to the statistical analysis. We greatly appreciate the generous administrative operations assistance from the Childhood Cancer Foundation, Taipei, Taiwan.

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