RESEARCH ARTICLE

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Predictors and Treatment Outcomes of Pediatric Osteosarcoma in Diverse Socioeconomic Backgrounds in Southeast Asia: A Retrospective Multicenter Study

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Abstract

Background: Pediatric osteosarcoma outcomes among developed and developing countries have not been previously compared. Countries in Southeast Asia (SEA) have a wide variety of socioeconomic statuses. A multi-institutional retrospective study was conducted to determine the prognostic factors and outcomes for pediatric osteosarcoma in SEA. **Methods:** Pediatric patients with osteosarcoma treated between 1998 and 2017 in 4 SEA pediatric oncology centers were studied. Countries were classified using the World Bank Atlas method. Kaplan–Meier method and Cox's Proportion Hazard Model were applied to estimate survival outcomes and identify prognostic factors. **Results:** In all, 149 patients with osteosarcoma with a mean age of 12.48±3.66 years were enrolled. The localized to metastatic disease ratio was 1.5:1. The 5-year overall survival (OS) and event-free survival (EFS) were 53.8% and 42%, respectively. Prognostic factors associated with outcomes were country, stage of disease, MTX-containing regimens, and surgery type (p-value <0.05). In patients with localized disease, EFS was superior with limb-salvage surgery (62%) than amputation or rotationplasty (40%) (p-value 0.009). MTX-containing chemotherapies provided higher OS (45.3%) and EFS (37.9%) than non-MTX regimens (12.3% and 10.7%, respectively) among metastatic patients (p-value 0.004 and 0.005, respectively). Metastatic disease was an independent prognostic factor for death but not relapse outcome. **Conclusion:** The disease outcomes in SEA were acceptable compared to developed countries. The stage of disease was the only independent prognostic factor. MTX-containing regimens and limb-salvage surgery should be considered where possible.

Keywords: Osteosarcoma- Southeast Asia- metastasis- methotrexate- limb salvage

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Introduction

Osteosarcoma is the most common primary malignant bone tumor among children and adolescents (Mirabello et al., 2009). Peak age incidence is the pubertal period, correlating to the pubertal growth spurt (Geller and Gorlick 2010; Luetke et al., 2014) with relatively high incidence in Asian/Pacific populations (Mirabello et al., 2009). Established prognostic factors include primary sites and size of tumors, surgery (Fu et al., 2020), metastatic

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diseases, and tumor necrotic response after neoadjuvant chemotherapy (Abou Ali et al., 2019). Standard treatment for pediatric osteosarcoma in developed countries includes neoadjuvant methotrexate (MTX)-based chemotherapy followed by surgical control and subsequently adjuvant chemotherapy with desirable outcomes (Marina et al., 2016). However, in developing settings, non-MTX-based regimens predominate (Bajpai et al., 2017).

Management of osteosarcoma requires a complex multidisciplinary care team with advanced supportive care infrastructure (Othman et al., 2020). The outcomes of disease are distinct across territories. In countries with limited resources, outcomes are significantly poorer (Wiromrat et al., 2012) and most patients receive suboptimal treatment given chemotherapy shortage and unavailability of MTX plasma level monitoring (Choeyprasert et al., 2013; Choeyprasert et al., 2014), large tumor or late presentation (Puri et al., 2018), treatment abandonment, higher rates of metastasis (Friedrich et al., 2013), higher infection rates and disputative types of surgery (Qi et al., 2020).

Southeast Asia (SEA) consists of the ten countries which are defined as those with a gross national income (GNI) per capita in the year 2021, classified using the World Bank Atlas method in low (LIC), lower middle (LMIC), upper middle (UMIC) and high income (HIC) countries (The World Bank 2021). A marked diversity can be observed regarding socioeconomics and health care among SEA countries, from economic domination like Singapore to poorer nation status such as Cambodia (Chongsuvivatwong et al., 2011). The out-of-pocket expense discrepancy among countries is demonstrated. The out-of-pocket health expenditure range from 54% in the Philippines (LMIC), 31% in Singapore (HIC), to 11% in Thailand (UMIC) (The World Bank 2021). The economic status variables among these countries might affect a disparity in treatment and outcomes across the region.

The study of inter-ethnic variations in epidemiology, treatment, and outcomes of childhood osteosarcoma in SEA has been limited. Related reports have only addressed independent geographic areas (Noor et al., 2014; Pruksakorn et al., 2016). Accordingly, this study aimed to identify clinical characteristics, prognostic factors, and treatment outcomes as well as explore barriers to effective treatment of pediatric osteosarcoma in 4 oncology centers in SEA. The results of this study may lead to strategic treatment plans for the region which might improve the outlook for children with osteosarcoma among SEA.

Materials and Methods

Patient selection

The medical records of 208 pediatric patients with osteosarcoma who were newly diagnosed and treated primarily at four tertiary pediatric oncology institutions from three SEA countries between January 1, 1998, and December 31, 2017, were retrospectively reviewed. These centers were: Phramongkutklao Hospital, Bangkok, Thailand; Philippine General Hospital, Manila, the Philippines; KK Women's and Children's Hospital and National University Hospital, Singapore.

The study's inclusion criteria included patients with osteosarcoma from birth to 21 years old whose diagnosis of osteosarcoma was confirmed by histology. Patients with uncertain diagnoses, incomplete medical records, lost to follow up and abandoned treatment were excluded from the study.

Written informed consent and assent waived. The study was approved by the Institutional Review Board, Royal Thai Army Medical Department according to the ethics principles of the Declaration of Helsinki (1975) and its revision (reference number: IRBRTA 1747/2561); SingHealth Centralized Institutional Review Board (2018/2750).

Clinical definitions

Treatment abandonment was defined as failure to initiate or to complete treatment. This excluded the decision of palliative treatment or discontinued treatment due to toxicity by primary oncologists.

Maximal tumor diameter (MTD) was defined as the largest diameter of the tumor, assessed by either computed tomography (CT), or magnetic resonance imaging (MRI) depending on institutional availability.

Staging and disease evaluation

Disease evaluation and treatment response were assessed using CT, MRI, or technetium (Tc)-99m-methylene-diphosphonate (MDP) bone scintigraphy depending on institutional availability. Patients were initially radiologically staged according to pulmonary and bone metastatic disease criteria from the European and American Osteosarcoma (EURAMOS)-I Study (Smeland et al., 2019) and imaging guidelines for children with Ewing sarcoma and osteosarcoma from the Children's Oncology Group (COG) Bone Tumor Committee, respectively (Meyer et al., 2008).

Treatment

Different treatment protocols were used according to institutional preference. The treatment process consisted of either surgery alone or combined with chemotherapy.

Chemotherapy regimens

Patients, regardless of localize or metastatic stage, were treated as per existing protocols based on institutional experts' experiences and chemotherapy availability. Chemotherapy protocols included non-MTX protocols including the European Organization for Research and Treatment of Cancer (EORTC) 80931 protocol (cisplatin and doxorubicin [CD]) (Lewis et al., 2007), St. Jude Children's Research Hospital Osteosarcoma-99 (OS-99) Trial (carboplatin, doxorubicin, and ifosfamide [CDI]) (Daw et al., 2011) and adapted OS-99 regimen adding etoposide (CDIE), and MTX-containing regimens including EURAMOS-1 regimen (MTX, doxorubicin and cisplatin [MAP] with additional ifosfamide and etoposide [MAPIE]) (Marina et al., 2016), and Italian Sarcoma Group study for Osteosarcoma (ISG/OS)-1 (MTX, doxorubicin, cisplatin, and ifosfamide [MAPI]) (Ferrari et al., 2014).

Surgery

The surgical approach was indicated by the surgical experience in the individual institutions with curative or palliative intent. For limb-salvage surgery, resected bone was replaced with an implant, comprising either a bone graft or a metallic prosthesis.

Outcome definition

Overall survival (OS) was defined as the time duration from the date of diagnosis either to the time of death resulting from any causes or to the last follow-up for patients who survived.

Event-free survival (EFS) was defined as the time duration between the date of diagnosis and disease relapse, progression, or death, whatever came first, or the last follow-up for patients without events.

Statistical analysis

Overall demographic data, treatment strategies, and outcomes from all participating patients were analyzed using descriptive statistics, presented as mean with standard deviation (normal distribution) or median with range (nonnormal distribution) for continuous variables, and calculated using frequency and percentage for categorical variables. Countries were classified using the World Bank Atlas method (The World Bank 2021); the Philippines as LMIC, Thailand as UMIC, and Singapore as HIC and analyzed accordingly. Categorical and continuous variables were compared using Fisher's exact and One-Way ANOVA, respectively. Survival function was calculated using the Kaplan–Meier method and compared using Cox's Proportion Hazard Model. Cox's Proportion Hazard Model was used to evaluate the effect of covariates on hazard ratio (HR). Statistical and survival analyses were performed using STATA/IC, 16.0 Software, and a p-value <0.05 was considered statistically significant.

Results

Patient characteristics

Among the 208 patients with osteosarcoma eligible for the study, 59 (28%) were excluded due to loss to follow-up or abandoned treatment. Therefore, 149 patients were subsequently enrolled in this study.

Among 149 patients with osteosarcoma enrolled in this study, 33 (22.1%) patients were from Thailand (UMIC), 54 (36.2%) patients from the Philippines (LMIC), and 62 (41.6%) patients from Singapore (HIC). Patient characteristics including the age of diagnosis, MTD, primary sites, stage, sites of metastasis, chemotherapies, and surgery were analyzed according to the countries (Table 1).

The median age of diagnosis was 12.42 years. Median age of diagnosis among patients of the Philippines (14.42 years) was significantly older than Thailand (11.83 years) and Singapore (11.92 years) with p-value <0.001. Median MTD of patients from the Philippines (15 cm) was greater than patients of Thailand (9.5 cm) and Singapore (7.75 cm) with p-value <0.001. Localized to metastatic disease ratio was 1.5:1. Nevertheless, the stage of disease did not significantly differ between the three countries. However, the metastatic sites were different between countries with p-value 0.013.

In all, 144 (96.6%) patients received chemotherapy and those receiving neoadjuvant chemotherapy totaled 131 (91%) patients. However, neoadjuvant chemotherapy was more frequently delivered in Thailand (n=33, 100%) and Singapore (n=57, 95%) rather than the Philippines (n=41, 80.4%), with p-value 0.003. Overall, half (n=73, 50.7%) of patients received MTX-based chemotherapy, for which the majority was MAPIE (n=40, 27.8%). In addition, MTX-based regimens were applied in Thailand (n=30, 90.9%) and Singapore (n=43, 71.7%) while all patients in the Philippines received non-MTX protocols (p-value <0.001). CD regimen was the most commonly-used protocol among patients from the Philippines (n=39, 76.5%).

Surgery was performed in 136 (91.3%) patients. Nonetheless, limb salvage surgery was more frequently performed in patients from Thailand (n=24, 75%) and Singapore (n=41, 74.5%) than the Philippines (n=9, 18.4%), with p-value <0.001.

Overall treatment outcomes

Five-year OS (Figure 1A) and EFS (Figure 1B) were

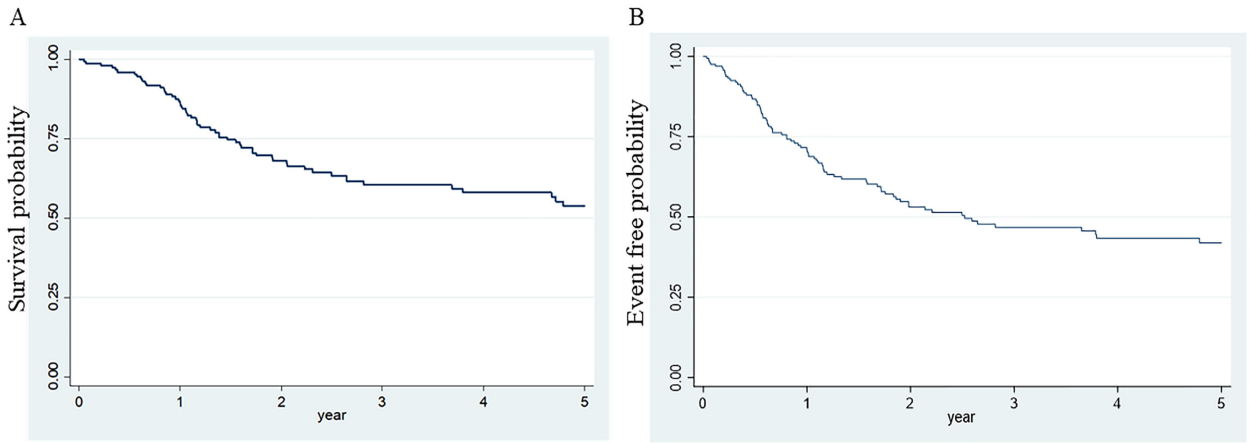

Figure 1. Overall Survival (A) and Event-Free Survival (B) of Pediatric Patients with Osteosarcoma (n=149). Note: Overall and event-free survival analysis was calculated using the Kaplan–Meier curves.

Table 1. Patient Demographic Data (n=149)

	Thailand (n=33) N (%)	The Philippines (n=54) N (%)	Singapore (n=62) N (%)	Total (n=149) N (%)	p-value
Age of diagnosis (years)					<0.001
Mean±SD	10.88±3.41	13.91±3.15	12.09±3.78	12.48±3.66	
Median (range)	11.83 (2.33-15.58)	14.42 (5.25-18.42)	11.92 (5.33-21.58)	12.42 (2.33-21.58)	
Maximal tumor diameter (cm)					
Mean±SD	10.99±6.68	17.64±11.34	8.92±3.87	13.46±9.45	<0.001
Median (range)	9.5 (2-38)	15 (5-82)	7.75 (2.2-16.5)	12 (2-82)	
Primary site					0.82
Femur	16 (48.4)	30 (55.5)	29 (46.8)	75 (50.3)	
Tibia	11 (33.3)	16 (29.6)	16 (25.8)	43 (28.9)	
Humerus	2 (6.1)	6 (11.1)	10 (16.2)	18 (12.1)	
Fibula	2 (6.1)	1 (1.9)	2 (3.2)	5 (3.3)	
Radius	2 (6.1)	1 (1.9)	2 (3.2)	5 (3.3)	
Pelvis	0 (0)	0 (0)	1 (1.6)	1 (0.7)	
Vertebrae	0 (0)	0 (0)	1 (1.6)	1 (0.7)	
Skull	0 (0)	0 (0)	1 (1.6)	1 (0.7)	
Stage					0.053
Localized	20 (60.6)	25 (46.3)	43 (69.4)	88 (59)	
Metastasis	13 (39.4)	28 (51.9)	19 (30.6)	60 (40.3)	
Unknown	0 (0)	1 (1.8)	0 (0)	1 (0.7)	
Metastatic site					0.013
Lung	10 (76.9)	26 (92.9)	12 (63.2)	48 (80)	
Bone	3 (23.1)	0 (0)	2 (10.5)	5 (8.3)	
Combined	0 (0)	2 (7.1)	5 (26.3)	7 (11.7)	
Chemotherapy					0.072
Received	33 (100)	51 (94.4)	60 (96.8)	144 (96.6)	
Not received	0 (0)	3 (5.6)	0 (0)	3 (2.1)	
Unknown	0 (0)	0 (0)	2 (3.2)	2 (1.3)	
Neoadjuvant chemotherapy					0.003
Received	33 (100)	41 (80.4)	57 (95)	131 (91)	
Not received	0 (0)	10 (19.6)	3 (5)	13 (9)	
Chemotherapy regimen					<0.001
Non-methotrexate	3 (9.1)	51 (100)	17 (28.3)	71 (49.3)	
CD	3 (9.1)	39 (76.5)	12 (20)	54 (37.5)	
CDIE	0 (0)	12 (23.5)	0 (0)	12 (8.3)	
CDI	0 (0)	0 (0)	5 (8.3)	5 (3.5)	
Methotrexate-based	30 (90.9)	0 (0)	43 (71.7)	73 (50.7)	
MAPIE	9 (27.3)	0 (0)	31 (51.7)	40 (27.8)	
MAPI	7 (21.2)	0 (0)	9 (15)	16 (11.1)	
MAP	12 (36.4)	0 (0)	0 (0)	12 (8.3)	
Others	2 (6)	0 (0)	3 (5)	5 (3.5)	
Surgery					0.462
Surgery	32 (97)	49 (90.7)	55 (88.7)	136 (91.3)	
No surgery	1 (3)	5 (9.3)	3 (4.8)	9 (6)	
Unknown	0 (0)	0 (0)	4 (6.5)	4 (2.7)	
Type of surgery					<0.001
Limb salvage	24 (75)	9 (18.4)	41 (74.5)	74 (54.4)	
Amputation	8 (25)	35 (71.4)	14 (25.5)	57 (41.9)	
Rotationplasty	0 (0)	5 (10.2)	0 (0)	5 (3.7)	

Notes: Data are presented as mean±SD for continuous variables and number (%) for categorical variables. Comparison between two independent data sets were analyzed using Fisher's exact test or One-Way ANOVA (age at diagnosis and maximal tumor diameter). P-value <0.05 is considered as statistical significance. Abbreviations: CD, cisplatin and doxorubicin; CDI, carboplatin; doxorubicin, and ifosfamide; CDIE, carboplatin; doxorubicin, ifosfamide, and etoposide; cm, centimeter(s); MAP, methotrexate;-doxorubicin and cisplatin; MAPI, methotrexate, doxorubicin, cisplatin, and ifosfamide; MAPIE, methotrexate, doxorubicin and cisplatin, ifosfamide, and etoposide, SD; standard deviation

Table 3. Overall and Event-Free Survivals by Chemotherapy Regimens and Types of Surgery in Localized vs. Metastatic Osteosarcoma Patients (n=149)

Stage	Factors		5-year OS (%)				5-year EFS (%)			
		OS (%)	95%CI (%)	HR	95%CI	p-value	EFS (%)	95%CI (%)	HR	95%CI	p-value
Localized	Chemotherapy regimen										
	Non-methotrexate	60.3	38.6-76.4	2.515	0.971-6.517	0.057	45.8	26.2-63.5	1.647	0.836-3.244	0.149
	Methotrexate-based	80	61.3-90.3	1			65.8	49.2-78.1	1		
	Type of surgery										
	Amputation/Rotationplasty	60.8	38.5-77.2	2.153	0.908-5.106	0.082	39.9	22.5-56.8	2.331	1.237-4.39	0.009
	Limb salvage	72.8	55.2-84.4	1			62.2	45.2-75.2	1		
Metastasis	Chemotherapy regimen										
	Non-methotrexate	12.3	2.3-31.2	2.918	1.402-6.069	0.004	10.7	2-27.9	2.610	1.33-5.124	0.005
	Methotrexate-based	45.3	23-65.2	1			37.9	18.7-57.1	1		
	Type of surgery										
	Amputation/Rotationplasty	29.4	12.8-48.1	1.918	0.882-4.17	0.1	25.8	10.9-43.7	1.101	0.561-2.158	0.78
	Limb salvage	37	13.1-61.4	1			29.8	10.5-52.3	1		

Notes: Survival function was calculated using the Kaplan–Meier method and compared using Cox's Proportion Hazard Model. P-value <0.05 is considered as statistical significance; Abbreviations: CI, confidence interval; EFS, event-free survival; HR, Hazard ratio; OS, overall survival

Table 2. Overall and Event-Free Survivals of Pediatric Patients with Osteosarcoma (n=149)

Factors	N(%)	5-year OS (%)					5-year EFS (%)				
		OS (%)	95%CI (%)	HR	95%CI	p-value	EFS (%)	95%CI (%)	HR	95%CI	p-value
Country											
Thailand	33 (22.1)	70.9	48.4-85	1			59.5	39.9-74.6	1		
The Philippines	54 (36.2)	20.3	7.4-37.8	4.81	2.148-10.774	<0.001	15.3	4.7-31.7	3.707	1.932-7.114	<0.001
Singapore	62 (41.6)	65.8	51-77.1	1.152	0.5-2.653	0.739	52.1	38.1-64.4	1.292	0.677-2.465	0.435
Stage											
Localized	88 (59.5)	69.6	56.4-79.5	1			53.4	41.3-64	1		
Metastasis	60 (40.5)	28.4	15.4-42.7	3.742	2.167-6.46	<0.001	23.8	12.6-36.9	2.365	1.537-3.638	<0.001
Chemotherapy regimen											
Non-methotrexate	71 (49.3)	39.4	25.3-53.1	2.698	1.526-4.77	0.001	29.7	17.4-43	2.009	1.272-3.172	0.003
Methotrexate-based	73 (50.7)	68	53.7-78.7	1			55.8	42.7-67.1	1		
Type of surgery											
Amputation/Rotationplasty	62 (45.6)	45.4	30.8-58.9	2.382	1.348-4.209	0.003	32.6	20.6-45.2	1.974	1.251-3.114	0.003
Limb salvage	74 (54.4)	63.7	49-75.1	1			53.3	39.6-65.3	1		

Notes: Survival function was calculated using the Kaplan–Meier method and compared using Cox's Proportion Hazard Model. P-value <0.05 is considered as statistical significance; Abbreviations: CI, confidence interval; EFS, event-free survival; HR, Hazard ratio; OS, overall survival

53.8% (95% confidence interval [CI], 43.9% to 62.7%) and 42% (95% CI, 33.1% to 50.6%), respectively. Relapse or disease progression occurred among 59 patients (39.6%). Twenty-two (37.3%) patients experienced disease progression while receiving treatment, 33 (55.9%) patients had a recurrence of disease after the end of treatment, and 4 (6.8%) patients showed unknown timing of disease recurrence. At the end of the study, 87 (58.4%) patients were alive, with 74 (85.1%) patients surviving without disease and 13 (14.9%) patients living with disease. Sixty-two (41.6%) patients expired. Fifty-one (82.3%) patients died from disease progression or relapse and 11 (17.7%) patients died from other causes including infection, electrolytes imbalance, secondary leukemia and cardiomyopathy.

Five-year OS (Figure 2A) and EFS (Figure 2B) of patients from Thailand and Singapore did not significantly differ. Compared to Thailand (OS of 70.9% and EFS of 59.5%), patients from the Philippines had a significantly lower 5-year OS of 20.3% (p-value <0.001) and EFS of 15.3% (p-value <0.001) as shown in Figure 2.

Five-year OS of localized and metastatic patients were 69.6% versus 28.4% with p-value <0.001, and EFS were 53.4% versus 23.8% with p-value <0.001.

Regarding chemotherapy regimens, 5-year OS of MTX and non-MTX-based regimens were 68% versus 39.4% with p-value 0.001, and EFS were 55.8% versus 29.7% with p-value 0.003.

Five-year OS of patients undergoing limb salvage surgery and amputation or rotationplasty were 63.7%

Table 4. Multivariable Analysis of Risk Factors Associated with Outcomes in Pediatric Osteosarcoma Patients (n=149)

	N(%)	Death					Relapse					
		Crude			Adjusted		Crude			Adjusted		
		HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Country													
Thailand	33 (22.1)	1			1			1			1		
The Philippines	54 (36.2)	4.81	2.148-10.774	<0.001	0.503	0.053-4.81	0.551	2.801	1.331-5.898	0.007	0.215	0.027-1.689	0.144
Singapore	62 (41.6)	1.152	0.5-2.653	0.739	0.61	0.3178-2.087	0.431	1.105	0.527-2.317	0.791	0.637	0.243-1.667	0.358
Stage													
Localized	88 (59.5)	1			1			1			1		
Metastasis	60 (40.5)	3.742	2.167-6.460	<0.001	3.196	1.612-6.336	0.001	1.8	1.073-3.02	0.026	1.879	0.974-3.626	0.06
Chemotherapy regimen													
Non-methotrexate	71 (49.3)	2.698	1.526-4.77	0.001	3.542	0.255-49.249	0.346	2.228	1.302-3.812	0.003	1.648	0.151-18.008	0.682
Methotrexate-based	73 (50.7)	1			1			1			1		
Type of surgery													
Amputation/Rotationplasty	62 (45.6)	2.382	1.348-4.209	0.003	1.09	0.439-2.707	0.852	1.722	1.022-2.9	0.041	1.07	0.483-2.372	0.867
Limb salvage	74 (54.4)	1			1			1			1		

Notes: Outcomes were addressed at 5-year from diagnosis. Univariate analysis and multivariate analysis were calculated using Cox's Proportion Hazard Model. P-value <0.05 is considered as statistical significance; Abbreviations: CI, confidence interval; HR, Hazard ratio

versus 45.4% with p-value 0.003, and EFS were 53.3% versus 32.6% with p-value 0.003. OS and EFS among patients with osteosarcoma according to country, stage of disease, chemotherapy regimens, and types of surgery are summarized in Table 2.

Outcomes of localized vs. metastatic osteosarcoma patients

Among patients with localized disease, 5-year OS did not differ according to MTX-based chemotherapy regimens or nature of surgery. However, the EFS of patients experiencing limb salvage surgery (62.2%) was significantly higher than those with amputation or rotationplasty (39.9%) with p-value 0.009.

In patients with metastatic disease, those receiving MTX-based regimens had significantly higher 5-year OS and EFS (45.3% and 37.9%, respectively) than patients without MTX (12.3% and 10.7%, respectively) with p-value 0.004 and 0.005, respectively.

However, OS and EFS did not differ significantly between metastatic patients experiencing limb salvage surgery and amputation or rotationplasty. Outcomes between localized versus metastatic osteosarcoma patients were described in Table 3.

Factors associated with outcomes in pediatric osteosarcoma

Countries, stage of disease, chemotherapy protocols, and types of surgery were significantly associated with death and relapse outcomes at univariate analysis with p-values <0.05. On subsequent multivariate analysis, disease stage remained the only independent risk factor significantly associated with survival outcome with p-value 0.001 (adjusted HR, 3.196; 95% CI, 1.612 to 6.336) (Table 4).

Discussion

This study represents the first multicenter study of prognostic factors and associated outcomes of pediatric osteosarcoma in SEA, which is a unique geopolitical region with countries of diverse socioeconomic status, resulting in markedly differing management strategies and outcomes. Even though the data only included one country from each category and was limited to middle- and HIC, each country might represent the reality of countries in the same country classification. Few studies have evaluated treatment outcomes in low and middle income countries (LMC) such in the Asia-Pacific (Noor et al., 2014; Abou Ali et al., 2019; Bajpai et al., 2019) and in South Africa (Vasquez et al., 2016).

Osteosarcoma is the most common musculoskeletal malignancy with a high rate in Asian/Pacific Islander populations at the mean age of 13 years in this study which was similar to related studies in a developing country (Pruksakorn et al., 2016) or North America (Mirabello et al., 2009). Treatment abandonment is a major barrier in achieving desirable outcomes in LMC. Interestingly, MTD, especially among LMIC patients, was extremely large (Puri et al., 2018). This finding was likely related to delayed diagnoses, one of the crucial barriers to effective treatment of pediatric solid tumors (Loh et al., 2009). Diagnostic delay has also been associated with older age at diagnosis and nature of first local healthcare contact (Loh et al., 2012), which are significant factors that impact outcomes. Moreover, among the Philippines patients, we found a higher incidence of metastatic disease at diagnosis - a factor that may have further contributed to their observed outcomes.

Some limitations were encountered in terms of resource availability, supportive care contexts (Rastogi et al., 2018) as well as disease burdens including tremendous tumors or metastatic disease in a resource-constrained

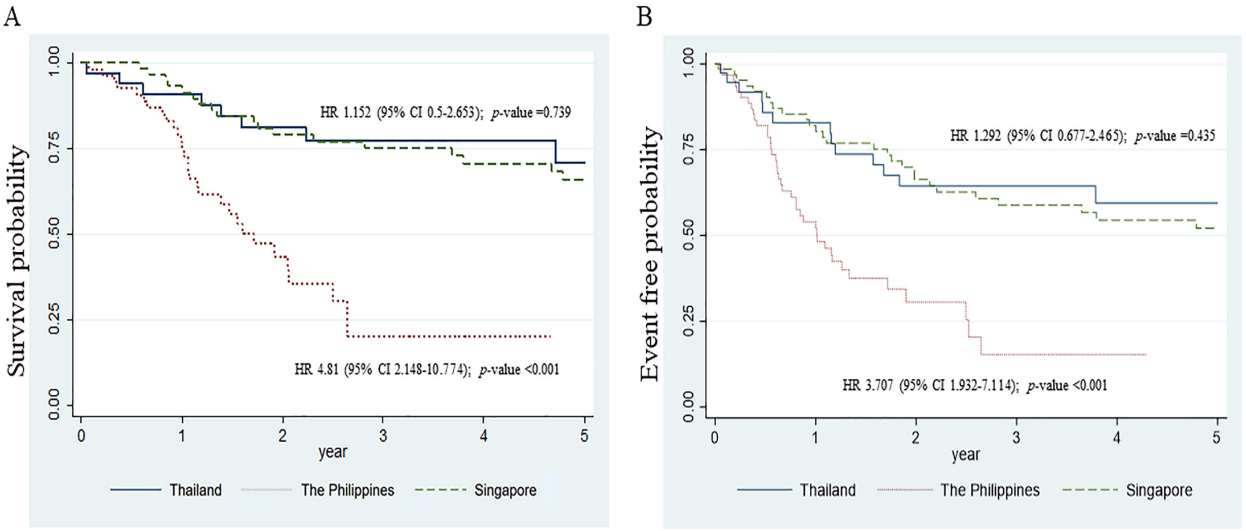

Figure 2. Overall Survival (A) and Event-Free Survival (B) of Pediatric Patients with Osteosarcoma (n=149) According to Countries. Notes: Survival function was calculated using the Kaplan–Meier method and compared using Cox's Proportion Hazard Model. P-value <0.05 is considered as statistical significance. Abbreviations: CI, confidence interval; HR, Hazard ratio

setting. These limitations challenge the local experts to adapt treatment from standard treatment to upfront surgery, followed by adjuvant chemotherapy.

MTX-based regimens have been shown data to substantially improve outcomes in pediatric osteosarcoma (Bacci et al., 1993). Although high dose MTX protocols have become the standard of treatment for pediatric osteosarcoma in developed countries, yet non-MTX containing regimens may still be more suitable and tolerable with desirable outcomes (Daw et al., 2011) especially in resource-constrained countries (Choeyprasert et al., 2013; Bajpai et al., 2017). MTX may associate with an increased admission rate and higher cost of treatment which lead to treatment abandonment (Verma et al., 2021). Therefore, non-MTX-containing regimens may be preferred in centers without MTX monitoring capabilities or bed occupancy limitations, but an assessment of risks and benefits is required to identify optimal treatment approaches to achieve the best outcomes in such settings.

Amputation is typically preferred over limb salvage for patients with older age, advanced stage, large tumor size, comorbidities and low socioeconomic status (Evans et al., 2020), such as in LMC. In addition, amputation is more often performed among metastatic patients in LMIC (Pakos et al., 2009; Noor et al., 2014). While significantly superior outcomes were observed in our patients who underwent limb salvage surgery than amputation, this finding may be confounded by the improved supportive care and adjuvant therapy in Singapore and Thailand in our study (Evans et al., 2020; Qi et al., 2020). Nonetheless, amputation may still be appropriate in resource-limited contexts, as it effectively lowers the rate of local recurrence (Nakamura et al., 2020) while preserving adequate functional outcomes and quality of life (Solooki et al., 2018).

Although the outcomes for pediatric osteosarcoma in SEA seemed to be comparable to that of developed countries, this would be optimistic due to the high rate of abandonment that was not incorporated in survival analysis. Notably, 5-year OS was closed to 5-year EFS, especially in metastatic patients in this study. The observation is likely related to being unable to achieve disease remission after encountering disease relapse and experiencing treatment-related toxicity including post-chemotherapy electrolyte disorders and infection. Increased treatment-related mortality (TRM) has been reported in patients treated in LMIC (Bajpai et al., 2019; Totadri et al., 2020) and receiving non-MTX regimens (Bajpai et al., 2019).

Outcomes between localized and metastatic osteosarcoma were diverse. The outcomes for localized osteosarcoma who completed treatment using CD and MTX containing regimens in SEA institutions were similar to long-term data from European Osteosarcoma Intergroup (Whelan et al., 2012) and EURAMOS (Smeland et al., 2019). MTX-based chemotherapy enhanced OS and EFS in metastatic diseases. Patients with metastatic disease experienced non-relapse mortality for which MTX-containing chemotherapy should be substituted to decrease the mortality rate. Toxicities from non-MTX chemotherapies included electrolyte imbalance (Daw et al., 2011), bone marrow suppression (Patel et al., 2002) and secondary leukemia. Ifosfamide and etoposide have been reported to increase the risk of non-hematological toxicity (Marina et al., 2016). However, limb salvage surgery was related to superior EFS among localized osteosarcoma patients. Although most patients suitable for limb salvage surgery probably had localized and smaller tumors amenable for this technique while patients with metastatic or large tumors needed to be amputated, alternative factors might be a reflection of surgical experience in limb salvage surgery or financial affordable of the family.

Univariate prognostic factors related to OS and EFS were countries, stage of disease (Fu et al., 2020), MTX-containing regimens and surgery types (Pakos

et al., 2009), while the metastatic disease was the only independent prognostic factor for OS, but not relapse.

Therefore, the recommended treatment approaches for pediatric osteosarcoma in SEA should be tailored by disease stage. In localized disease, limb salvage surgery could be beneficial where possible. For metastatic disease, high dose MTX might be feasible (Choeyprasert et al., 2014) and tolerable to decrease treatment toxicity such as late effects of chemotherapy from alkylators and eventually decrease disease-associated mortality (Choeyprasert et al., 2014). Supportive care and appropriate hydration strategies can prevent side effects in a resource-constrained setting with limited capabilities to monitor plasma MTX level (Traivaree et al., 2018).

Strategies to improve treatment outcomes for pediatric patients with osteosarcoma in countries with limited resources include promoting early diagnosis, improving supportive care to reduce TRM (Yadav et al., 2014), increasing access and widening insurance coverage (Perez-Cuevas et al., 2013) for lowering abandonment, enhancing multidisciplinary care management (Friedrich et al., 2014), and encouraging more multi-institutional studies to address the treatment barriers (Rodriguez-Galindo et al., 2015).

Limitations of the study

This study was a retrospective study in which data collection might not have been uniform. The study included patients from three countries which might not represent the entire population of SEA, especially lack of LIC data. The diagnostic time which would associate with MTD, outcomes, and treatment abandonment was not explored. Data of grafts or prostheses among patients undergoing limb salvage surgery was largely unavailable. Different durations and heterogenicity of treatment could also have affected the outcomes.

In conclusion, the overall outcomes for pediatric patients with osteosarcoma in SEA were acceptable compared to developed countries, but abandonment should be taken into account. The stage of disease was the only independent prognostic factor to define survival but not recurrent outcomes. MTX-containing regimens are recommended to improve survival and prevent disease recurrence. Limb salvage is encouraged particularly among localized patients where possible. However, this advice on risk-adjusted determination on best surgical approach, depending on available surgical resources and financial capabilities.

Author Contribution Statement

CM conceptualized and designed the study, analyzed and interpreted data and was a major contributor in writing the manuscript. APA assisted with concept development and analyzed and interpreted data. AHPL, SYS assembled the data and assisted with data interpretation. SB served as an administrative supporter and coordinator. CL and CRG assisted in conceptualizing and designing the study. All authors contributed to patient care, collected data, and critically reviewed and approved the final manuscript.

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Ethics approval

The study was approved by the Institutional Review Board, Royal Thai Army Medical Department according to the ethics principles of the Declaration of Helsinki (1975) and its revision (reference number: IRBRTA 1747/2561); SingHealth Centralized Institutional Review Board (2018/2750).

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Scientific content approval

The manuscript was reviewed and approved by the Office of Research and Development, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand.

Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy or ethical restriction. The data are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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