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Survival rate and prognostic factors of conventional osteosarcoma in Northern Thailand: A series from Chiang Mai University Hospital

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ABSTRACT

Background: Osteosarcoma is a common and aggressive primary malignant bone tumor occurring in children and adolescents. It is one of the most aggressive human cancers and the most common cause of cancer-associated limb loss. As treatment in Thailand has produced a lower survival rate than in developed countries; therefore, this study identified survival rate and the poor prognostic factors of osteosarcoma in Northern Thailand.
Methods: The retrospective cases of osteosarcoma, diagnosis between 1 January 1996 and 31 December 2013, were evaluated. Five and ten year overall survival rates were analyzed using time-to-event analysis. Potential prognostic factors were identified by multivariate regression analysis.
Results: There were 208 newly diagnosed osteosarcomas during that period, and 144 cases met the criteria for analysis. The majority of the osteosarcoma cases (78.5%) were aged 0–24 years. The overall 5- and 10-year survival rates were 37.9% and 33.6%, respectively. Presence of metastasis at initial examination, delayed and against treatment co-operation, and axial skeletal location were identified as independent prognostic factors for survival, with hazard ratios of 4.3, 2.5 and 3.8, and 3.1, respectively.
Conclusions: This osteosarcoma cohort had a relatively poor overall survival rate. The prognostic factors identified would play a critical role in modifying survival rates of osteosarcoma patients; as rapid disease recognition, a better treatment counselling, as well as improving of chemotherapeutic regimens were found to be important in improving the overall survival rate in Thailand.

1. Introduction

Osteosarcoma, a common primary malignant bone tumor in children and adolescents [1,2], is one of the most aggressive human cancers and is the most common cause of cancer associated limb loss [3]. Metastasis of tumor is frequently occur in lung and bone which is the main cause of death for disease [4]. This cancer has a bimodal distribution, appearing more frequently in the youth (age 0–24 years) and in the elderly (age more than 60 years) [1,5,6]. Worldwide, an average incidence rate of the youth was 3.4 per million with a male to female ratio of 1.4:1. Osteosarcoma mostly originate in long bone such as distal femur, proximal tibia and humerus during the rapid growing process [7].

Outcome of osteosarcoma treatment has improved over the past thirty years due to the use of adjuvant chemotherapy combined with surgery [8,9]. Despite of using multimodal chemotherapeutic regimens including Adriamycin, Cisplatin, Ifosfamide, and Metrotrexate, the five year survival rates of osteosarcoma patients have reached a plateau at approximately 62–70% [10–13]. Treatment in Thailand has produced a lower survival rate (47% of 3-year overall survival rate) than in other developed countries [14,15]. There are two main categories of previously described poor prognostic factors; (1) the patient factors including primary metastasis, large tumor size, high level of alkaline phosphatase, age $\leq$ 14 years old, and axial location; and (2) the treatment factors including poor chemotherapeutic response, positive surgical margin, and using two drugs regimen of chemotherapy [4,16–18].

Abbreviation: CI, confident interval; CMU-PAC, Chiang Mai University-Picture Archive Communication; COSS, The Cooperative Osteosarcoma Study; CT, computer tomography; HR, hazard ratio; MRI, magnetic resonance imaging; N, number; Q, quartile range; SMI, Saundok Medical Informatics; OS, overall survival; RR, risk ratio.

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In addition to the biology of the disease, other variables might affect treatment outcomes including familial acceptance, management time, level of cooperation with treatment, and personal beliefs. The studies in various aspects of this disease are needed to identify important prognostic factors, particularly the factors that are potentially adjustable, in order to improve the quality of life and overall survival rate in Thailand. Herein, we identified the survival rate and important prognostic factors for osteosarcoma in Northern Thailand.

2. Materials and methods

2.1. Patients

A retrospective study was conducted at Chiang Mai University Hospital, a tertiary center which cares for musculoskeletal tumor patients from the eight upper north provinces of Thailand (Chiang Mai, Chiang Rai, Mae Hong Son, Lampang, Lamphun, Phayao, Nan and Phrae) as well as most cases from the lower north provinces (Uttaradit, Tak, Sukhothai, Kamphaeng Phet, Phitsanulok, Phetchabun, and Phichit). Data were collected from various sources including (1) Chiang Mai Cancer Registration, Chiang Mai University Hospital Registration Department (ICD10; code: malignant bone cancer, and osteosarcoma); (2) Musculoskeletal Oncology Database (provided by Dr. Olarn Arpornchayanon); (3) Musculoskeletal pathology Database (provided by Dr. Jongkolnee Settakorn); (4) Digicard of Chiang Mai University Hospital which include out and in patient history; (5) Saundok Medical Informatics (SMI) systems which included diagnostic and laboratory results; and (6) Chiang Mai University-Picture Archive Communication (CMU-PAC) system which included radiographic information. This study was approved by the Ethical Committee of Chiang Mai University Hospital.

2.2. Treatment protocol of osteosarcoma

The treatment protocol for osteosarcoma has been consistent since 1996. Patients who suspected osteosarcoma based on history, physical examination, and plain radiography were entered into the osteosarcoma investigation and treatment protocol. Magnetic resonance imaging (MRI) was performed within 2 weeks after enrollment. Incisional biopsy was performed within one week after MRI. Definite pathological result was reported within two weeks following the biopsy. During that period, complete systemic staging including CT-chest and bone scans were performed. Results were available within one month of diagnosis. The treatment plan, implemented by multidisciplinary team, was started within the week after receipt of the pathological report. Neoadjuvant chemotherapy was started followed by surgery and adjuvant chemotherapy in salvageable cases. Amputation followed by adjuvant chemotherapy was implemented when salvage procedures were not able to be performed. For adolescent and adult patients (>15 years of age), the first line chemotherapy was Doxorubicin (50 mg/m^2) and Cisplatin (80 mg/m^2) at an interval of 3–4 weeks for three cycles as neoadjuvant therapy, then followed by another 3 cycles for adjuvant therapy. For pediatric patients (<15 years old), the first line chemotherapy was Carboplatin (400 mg/m^2/dose on day1) and Doxorubicin (20 mg/m^2/day on day 1–3) at an intervals of 3–4 weeks for three cycles as neoadjuvant therapy, then followed by another 3 or 4 cycles of Carboplatin and Doxorubicin for adjuvant therapy [14].

2.3. Assessment of patients, tumors and treatment related variables

Variables evaluated in this study for their possible role in the outcome of osteosarcoma patients included age, anatomical location of the cancer, diagnosis delay, treatment delay, tumor volume (the two longest dimensions (d1 and d2) as measured from MRI, volume was calculated using the formula $V = 4/3\pi r^3$, with $r = {}^1/_2(d1 + d2)^{1/2}$ [19]), clinical symptom presentation, systemic metastasis at initial presentation and level of cooperation with treatment. The level of cooperation with treatment was divided into three different groups. The "Complied Group" included patients who were able to accept all medical advices, i.e., three courses of neoadjuvant chemotherapy followed by surgery and adjuvant for limb salvageable cases; and amputation or rotationplasty with 6 courses of adjuvant chemotherapy for unsalvageable cases. Cases in which a delay of over 1 month occurred for any reasons in any of steps were placed in the "Delayed Group". Cases with a delay of more than three months in any of the steps and those who refused both chemotherapy and surgery were considered to be in the "Against Group". Median overall survival was calculated in months from the date of diagnosis (the date of pathological report) until the date of death, loss to follow up, or end of the study 31 December 2014.

2.4. Statistical analysis

Time-to-event analysis of 144 cases with reliable data was performed using Kaplan–Meier curve to identify the 5- and 10-year survival rates. Differences in median survival rates for each variable were analyzed by Log-rank test. Multivariate survival analysis was conducted using Cox's regression model to identify

Table 1
Baseline patient characteristics of osteosarcoma.

Characteristics	Number (%)
Total	144 (100)
Age, years	
<13 years	44 (30.6)
≥13 years	100 (69.4)
Gender	
Male	79 (54.9)
Female	65 (45.1)
Locations (number, %)	
Axial skeleton	15 (10.4)
Upper extremities[a]	17 (11.8)
Lower extremities	112 (77.8)
Diagnosis delay, weeks	
<22 weeks	108 (75.0)
≥22 weeks	36 (25.0)
Treatment delay, weeks	
<6 weeks	99 (68.7)
≥6 weeks	45 (31.3)
Tumor volume, mL	
<180 mL	69 (47.9)
≥180 mL	75 (52.1)
Pathological fracture	
Present	11 (7.6)
Absent	113 (92.4)
First clinical presentation	
Pain	106 (73.6)
Not pain	38 (26.4)
Initial metastasis status	
Non-metastasis	66 (45.8)
Metastasis	78 (54.2)
Co-operative of treatment	
Complied	96 (66.7)
Delayed	38 (26.4)
Against	10 (6.9)
Type of surgery	
Amputation	78 (54.2)
Limb salvage surgery	47 (32.7)
Rotationplasty	2 (1.3)
No surgery	17 (11.8)

[a] Upper extremities and scapula.