FIVE-YEAR SURVIVAL AND PROGNOSTIC FACTORS OF OSTEOSARCOMA PATIENTS IN HOSPITAL UNIVERSITY SAINS MALAYSIA: AN ELEVEN YEAR REVIEW

by

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LIST OF ABBREVIATIONS

A	accrual time
AFT	accelerated failure time
AJCC	American Joint Commission on Cancer
ALP	Alkaline Phosphatase
CI	confidence interval
COSS	German-Austrian-Swiss Cooperative Osteosarcoma Study Group
CT scan	computed tomography scan
df	degree of freedom
DFS	Disease Free Survival
F	additional follow up time after end of recruitment
G	grade
G0	grade 0
G1	low grade
G2	high grade
h(t)	hazard function
HR	hazard ratio
HUSM	Hospital Universiti Sains Malaysia
LDH	Lactate Dehydrogenase
ICD-9-CM	International Classification of Disease Clinical Modification 9th Editions
ICD-10	International Classification of Disease for Oncology 10th editions
KM	Kaplan-Meier
LML	log-minus-log
LR	likelihood ratio
m	ratio of control to experimental patients
m_1	median survival time on control treatment
M	metastasis
M0	no metastatic
M1	regional or distant metastasis
MC	multicollinearity
MRI	magnetic resonance imaging
PH	proportional hazard
PO	proportional odds

PS	power and sample size calculation
R	detectable hazard ratio
RN	registration numbers
SD	standard deviation
SEER	The Surveillance, Epidemiology, and End Results
S(t)	survival function
SPSS	Statistical Package for Social Science
STATA	Statistics/Data Analysis
t	time
T	site
T0	benign tumor
T1	malignant tumor still confined within its anatomic compartment
T2	malignant tumor spread of the lesion beyond the anatomic compartment of origin of the tumor
TVC	time-varying covariate
UK	United Kingdom
USA	United State of America
VIF	variation inflation factor
WHO	World Health Organization

LIST OF SYMBOLS

$1-\beta$	power
α	level of significance
λ	lambda
n	sample
p	a shape parameter
$<$	less than
$\geq$	more than or equal
χ^2	chi-square
%	percentage

KADAR JANGKA HAYAT LIMA TAHUN DAN FAKTOR-FAKTOR PROGNOSTIK DI KALANGAN PESAKIT OSTEOSARCOMA DI HOSPITAL UNIVERSITI SAINS MALAYSIA: ULASAN SEBELAS TAHUN

ABSTRAK

PENGENALAN: Berdasarkan Pertubuhan Kesihatan Sedunia (WHO), anggaran insiden tahunan bagi osteosarcoma adalah kira-kira 4-5 per sejuta, berlaku biasanya pada dekad kedua kehidupan. Perbezaan demografi, budaya dan kepercayaan mungkin memberi perbezaan keputusan jangka hayat di Malaysia berbanding negara lain.

OBJEKTIF: Objektif kajian adalah untuk mengetahui kadar jangka hayat lima tahun di kalangan pesakit osteosarcoma yang dirawat semasa tempoh kajian, untuk mengenalpasti faktor-faktor prognostik yang mempengaruhi jangka hayat pesakit osteosarcoma dan untuk membuktikan model yang meramalkan jangka hayat pesakit osteosarcoma.

METODOLOGI: Ini adalah ulasan rekod secara retrospektif di mana data telah dikumpul daripada rekod perubatan pesakit yang melibatkan 127 orang pesakit osteosarcoma yang dirawat di HUSM, Kelantan. Fasa pengumpulan data bermula daripada 1 Ogos 1995 sehingga 31 Julai 2006 (sebelas tahun) dan penambahan masa tindakan susulan selama 12 bulan, selepas pengambilan peserta daripada 1 Ogos 2006 sehingga 31 Julai 2007, telah dimasukkan. Semua peserta yang memenuhi kriteria telah dimasukkan ke dalam kajian. Data pesakit osteosarcoma telah dikumpulkan daripada unit rekod perubatan menggunakan borang pengumpulan data. Status jangka hayat pesakit telah diperolehi daripada rekod perubatan begitu juga

dengan menghubungi saudara mereka melalui panggilan telefon atau melawat ke rumah dengan izin mereka. Analisis Kaplan-Meier dan 'Cox proportional hazard regression' telah digunakan di dalam analisis statistik.

KEPUTUSAN: Kadar kumulatif pertengahan jangka hayat masa untuk 127 pesakit osteosarcoma yang dirawat di HUSM adalah 47.77 bulan dan kadar kumulatif jangka hayat lima tahun adalah 48.94% (95% CI: 39.4; 57.8). Faktor-faktor prognostik yang mempengaruhi kematian pesakit osteosarcoma adalah jangka masa simptom (HR ubahsuai 0.34; 95% CI: 0.19; 0.61, nilai p=0.023), jenis pembedahan untuk tiada kes (HR ubahsuai 3.39; 95% CI: 1.85; 6.20, nilai p<0.001) dan jenis pembedahan bagi 'limb salvage' (HR ubahsuai 0.14; 95% CI: 0.07; 0.28, nilai p<0.001).

KESIMPULAN: Kadar jangka hayat lima tahun untuk pesakit osteosarcoma yang dirawat adalah agak rendah. Faktor-faktor prognostik yang dikenalpasti daripada kajian ini adalah sama dengan kajian lain. Jangka hayat pesakit osteosarcoma yang dirawat menjadi bertambah teruk jika jangkamasa simptom kurang daripada tujuh puluh hari, tidak menerima pembedahan atau menerima amputasi. Tetapi beberapa faktor prognostik tidak dapat dikenalpasti di dalam kajian ini.

FIVE-YEAR SURVIVAL RATE AND PROGNOSTIC FACTORS OF OSTEOSARCOMA PATIENTS IN HOSPITAL UNIVERSITY SAINS MALAYSIA (HUSM): AN ELEVEN YEAR REVIEW

ABSTRACT

INTRODUCTION: According to World Health Organization (WHO), the estimated annual incidence of osteosarcoma was approximately 4–5 per million peoples, occurring most commonly in the second decade of life. Differences in demography, culture and belief may give different results in survival for Malaysian compared to other countries.

OBJECTIVES: The objectives of this study were to determine the five-year survival rate of osteosarcoma patients treated during the study period, to identify the prognostic factors that influence the risk of death of osteosarcoma patients and to establish a model that predicts the survival of osteosarcoma patients.

METHODOLOGY: This was a retrospective record review study in which the data was collected from patients' medical records involving 127 patients diagnosed with osteosarcoma treated in HUSM, Kelantan. The recruitment phase of the participants began from 1st August 1995 till 31st July 2006 (11 years) and additional follow up period of 12 months, after the recruitment of subjects from 1st August 2006 till 31st July 2007, was included. All patients who fulfilled the criteria were included in the study. Data of osteosarcoma patients were collected from the medical record unit using data collection sheet. Patient's survival status was obtained from the medical record as well as contacting them or by home visit with their consent. The Kaplan-

Meier and Cox proportional hazard regression analyses were used in statistical analysis.

RESULTS: The overall median survival time for 127 patients with osteosarcoma treated was 47.77 months and the overall five-year survival rate was 48.94% (95% CI: 39.4; 57.8). The significant prognostic factors that influence the death in osteosarcoma were duration of symptoms (adjusted HR 0.34; 95% CI: 0.19; 0.61, *p* value=0.023), type of surgery for no cases (adjusted HR 3.39; 95% CI: 1.85; 6.20, *p* value<0.001) and type of surgery for limb salvage (adjusted HR 0.14; 95% CI: 0.07; 0.28, *p* value<0.001).

CONCLUSION: Five-year survival rate for osteosarcoma patients treated was acceptably low. The survival rate of osteosarcoma patients treated could be worse if the duration of symptoms were less than 70 days, not having a surgery or had been amputated. However, some important prognostic factors can not be identified in this study.

CHAPTER ONE: INTRODUCTION

Cancer is a frequent cause of death in both developing and developed countries, including Malaysia. It was proven as the third principle cause of death in Malaysian government hospital (Ministry of Health Malaysia, 2005). The same report also showed that this disease had become worse when a percentage of death increased from 9.54% in 2004 to 10.11% in 2005.

Amongst all cancer cases reported in Malaysia, bone cancer would not become the most diagnosed cancer in Malaysia like breast cancer or lung cancer. But the number of cases is still increases per year (Lim & Halimah., 2003). Many cases were not reported because the patients did not seek treatment at hospitals. Most of them would like to take traditional medicine than allopathic medicine.

In USA, bone sarcomas account for less than 0.2% of all malignancies, which equals an annual incidence of about 2600 cases (Jemal *et al.*, 2005). In western populations, malignant bone tumors account for 3–5% of cancers diagnosed in children less than 15 years of age (Parkin *et al*, 1998 cited from Stiller *et al.*, 2006a) and 7–8% of those in adolescents aged 15–19 years (Smith *et al*, 1999). Among South East Asian countries, in Thailand bone cancer accounted for 0.7% of all cancer cases in Chiang Mai University Hospital (Lorvidhaya & Srisukho, 1998 cited from Settakorn *et al.*, 2006).

According to World Health Organization (WHO) (2002), the estimated annual incidence of osteosarcoma was approximately 4–5 per million, occurring most commonly in the second decade of life (ages 11–20). Stiller *et al.* (2006a) reported that in European population that of 5572 cases, osteosarcoma was the most frequent subgroup, accounting for 52% of all registrations, while Ewing's sarcoma was second most frequent, accounting for 34% of cases. Chondrosarcoma and other specified tumors accounted for 6% and 4%, respectively, and 4% of registrations were for tumors of unspecified type. Osteosarcoma was slightly more common than Ewing's sarcoma, as shown by the ratio of numbers of cases (Parkin *et al.*, 1993).

In Hong Kong, where osteosarcoma was the most common primary bone cancer, the annual incidence was also approximately 1 per 100,000, constitutes 0.3% of all newly diagnosed cancers (Yip *et al.*, 1996). An epidemiologic study in Chiang Mai University Hospital, Thailand had recently reported a relatively high frequency of osteosarcoma (67%) among malignant non hematologic bone tumors between 2000 and 2004 (Settakorn *et al.*, 2007). They showed a higher frequency of osteosarcoma (67.4%, 58 out of 86) and lower frequencies of chondrosarcoma (11.6%, 10 out of 86) and Ewing sarcoma (3.5%, 3 out of 86) amongst the primary malignant bone tumors (Settakorn *et al.*, 2006).

Results of an epidemiologic survey of osteosarcoma in 1975 conducted in Malaysia showed that its incidence differed between the Malay and Chinese subpopulations, with 0.23 cases per 100,000 populations per year in the Chinese compared with 0.11 in the Malay. The incidence in the Indian subgroup was identical with that of the Chinese. It also was noted that the urban versus rural incidence in the Chinese was

0.31 versus 0.18, suggesting that environmental agents may be a factor (Silva & Subramanian, 1975 cited from Yip *et al.*, 1996).

According to Second National Cancer Registry in 2003, only 176 cases of bone cancer in Peninsular Malaysia had been reported at National Cancer Registry. The incidence was higher in male than female (55.1% versus 44.9%). Most of the cases in both gender groups were in the age range of 10-19 years old. However, not much information of bone cancer in Malaysia had been reported especially for osteosarcoma(Lim & Halimah., 2003).

According to Ajiki (2003), survival rates for total period from 1975 to 1994 of malignant bone tumor in childhood patients in Osaka, Japan was 52.8%. When compared a five-years relative survival rate from 1985 to 1994 in Osaka, England and Wales, and SEER, USA, their survival rate were 57.0% (95% CI:45.6–68.4), 51.0% and 66.9%. Survival rates for these three places are not much different. Five-year survival rate for European osteosarcoma patients were higher (58%) than survival rate for Ewing's sarcoma (42%) (Gatta *et al.*, 2003a).

A study by Bielack *et al.* (2002), the patient's age≥40 year old, sex, tumor site (tibia), primary metastases, prolonged symptoms before diagnosis, tumor size (large) and tumor response to preoperative chemotherapy were the prognostic factors of high grade osteosarcoma in German population. Study by Rech *et al.* (2004) in Brazil also considered age, volume, site, and resectability of the primary tumor, as well as serum LDH level and response to neoadjuvant chemotherapy as clinical characteristics with known prognostic importance.

This study was going to determine the five-year survival rate of osteosarcoma patients treated at HUSM and to identify the prognostic factors that influence the survival of osteosarcoma patients. Differences in demography, culture and belief may give different result in survival rate for Malaysian as compared to other country.

CHAPTER TWO: LITERATURE REVIEW

2.1 MALIGNANT BONE TUMOR

According to Cancer Reference Information from American Cancer Society (2006), malignant bone tumors spread to other tissues and organs. It's called metastases. It is life threatening and can not easily be cured by surgery. In addition to surgery, the treatment may include chemotherapy and radiotherapy. There are a few types of malignant bone tumor, which were osteosarcoma, Ewing's sarcoma and chondrosarcoma.

2.1.1 Osteosarcoma

The most common malignant bone cancer is osteosarcoma (also called osteogenic sarcoma) that is characterized by the production of osteoid or immature bone by the malignant cells. It is the most common bone cancer and the third most common malignancy in children and adolescents (10 to 20 years of age) (Wittig *et al.*, 2002). It classically arises in adolescents and becomes rare during middle age.

Osteosarcoma usually develops from osteoblast (the cells that make growing bone), that's why it most commonly affects teens who are experiencing a growth spurt. A study by Longhi *et al.* (2005) found that occurrence of osteosarcoma during adolescence is associated with a comparatively tall stature, but adult osteosarcoma patients do not display this association with height.

More males than females got this type of cancer. Osteosarcoma can develop in any bone, including the bones of the pelvis, shoulder, and jaw. The most common site is

around knee, with almost 70% of tumors being in the distal femur, proximal femur, proximal humerus and pelvis (Wittig *et al.*, 2002). Pelvic osteosarcoma and osteosarcoma arising in bones where surgery is difficult tend to have a poorer outcome.

2.1.2 Ewing's sarcoma

Second most common malignant bone cancer is Ewing's sarcoma. It typically appears in children or adolescents, but can also develop in the older population. Ewing tumors usually develop in bones, and less than 10% arise in other tissues and organs. They most often arise in the long bones of the legs and arms but may also develop in the pelvis and other bones.

2.1.3 Chondrosarcoma

Other malignant bone cancer is chondrosarcoma which arise in long and flat bones. It grows slowly and is often large at diagnosis. This cancer is uncommon in people younger than 20. After the age of 20 years old, the risk of developing chondrosarcoma continues to rise until reaching about 75 years. Men and women are equally likely to get this cancer.

Malignant fibrous histiocytoma and fibrosarcoma was other uncommon malignant bone cancers. These occur at soft tissue and are rare among children.

2.2 STAGING OF MALIGNANT BONE OF TUMOR

There are two ways that can be used to make staging of a malignant bone tumor, which are Enneking system and American Joint Commission on Cancer (AJCC) system.

The Enneking system of surgical staging of bone and soft tissue tumors is based on grade (G), site (T), and metastasis (M) and uses histologic, radiologic, and clinical criteria. It is the most widely used staging system and has been adopted by the Musculoskeletal Tumor Society.

In the Enneking system of grading of bone tumors, benign lesions are grade 0 (G0) and malignant lesions are either low grade (G1) or high grade (G2). Surgical grade generally follows histologic grade; however, a higher surgical grade may be applied if the radiographic features and clinical behavior of a lesion indicate aggressiveness incompatible with its benign histologic features.

In the Enneking system for assessing the site and local extent of bone tumors, T0 is reserved for benign tumors confined within a true capsule and the anatomic compartment of origin. An aggressive benign or malignant tumor still confined within its anatomic compartment is T1. T2 indicates spread of the lesion beyond the anatomic compartment of origin of the tumor.

In metastatic disease, M0 indicates no metastatic disease; M1 indicates regional or distant metastasis (Teo, 2007). Table 2.1 showed stage of malignant bone tumor by using Enneking system.

Table 2.1 Enneking System for Surgical Staging of Malignant Bone

Stage	Grade	Site	Metastasis
IA	G1	T1	M0
IB	G2	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

Adapted from Teo (2007)

Another system also used to stage all bone cancer is the American Joint Commission on Cancer (AJCC) system sixth edition (Greene *et al.*, 2002). This system is based on tumor grade and size and the presence and location of metastases. The stage is defined in Table 2.2 and Table 2.3.