SURVIVAL RATE AND PROGNOSTIC FACTORS OF EWING FAMILY TUMOR IN PAEDIATRIC PATIENTS (A 11-YEAR REVIEW) IN HOSPITAL USM FROM 2002-2012

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ACT	Actinomycin-D
AJCC	American Joint Committee on Cancer
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
BMA	Bone Marrow Aspiration
CAV/IE	Cyclophosphamide, Actinomycin, Vincristine/ Ifosfamide, Etoposide
CESS	Cooperative Ewing's Sarcoma Study
CI	Confidence Interval
CPM	Cylophosphamide
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
DXR	Doxorubicin
EFS	Event Free Survival
EFT	Ewing Family Tumor
EO	Extraosseous
ES	Ewing Sarcoma

ESR	Erythrocyte Sediment Rate
HPE	Histopathology Examination
HR	Hazard Ratio
HUSM	Hospital Universiti Sains Malaysia
ICD	International Classification of Disease
ICE	Ifosfamide, Carboplatin, Etoposide
IESS	Intergrouped Ewing's Sarcoma Studies Intergroup Ewing's Sarcoma
IFOS	Ifosfamide
LCH	Langerhans Cell Histiocytosis
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
MSK	Memorial Sloan Kettering
MTX	Methotrexate
OS	Overall Survival
PAS	Periodic Acid Schiff
PNET	Primitive Neuroectodermal Tumor
SEER	Surveillance, Epidemiology and End Result
SPSS	Statistical Package for the Social Science
USA	United State of America

VCR	Vincristine
VP 16	Etoposide

ABSTRAK

Pengenalan

Tumor Keluarga Ewing (EFT) merupakan tumor yang sangat malignan dan aggresif. Ia adalah tumor yang sangat jarang berlaku terutamanya di negara Asia jika dibandingkan dengan negara-negara barat. Sejak tiga dekad yang lalu, prognosis pesakit EFT telah berkembang dengan begitu pesat seperti yang telah dibuktikan dalam beberapa kajian klinikal, terutamanya disebabkan oleh perkembangan dalam rawatan kemoterapi. Di negara kita, tidak banyak data mengenai kadar jangka hayat dan keputusan akhir kanak-kanak EFT. Sehingga sekarang, belum ada kajian sebegini yang diterbitkan dari Hospital USM.

Objektif

Objektif kajian ini adalah untuk menilai kadar jangka hayat menyeluruh (OS) dan jangka hayat tanpa sebarang kejadian (EFS) di kalangan kanak-kanak yang menghidap Tumor Keluarga Ewing(EFT). Kami juga ingin mengkaji ciri-ciri demografik dan mengenalpasti faktor-faktor prognostik yang mempengaruhi EFS dan OS di kalangan kanak-kanak EFT yang dirawat di Hospital USM.

Kaedah Kajian

Kajian ini adalah kajian secara retrospektif melibatkan kanak-kanak yang berumur 0-18 tahun yang didiagnosa sebagai EFT. Kanak-kanak dikenal pasti melalui data pendaftaran di Unit Onkologi dan Unit Rekod Hospital USM. Pesakit yang meninggal, hilang atau tidak dapat dihubungi, surat dihantar ke Jabatan Pendaftaran Negeri untuk mendapatkan maklumat mengenai status akhir. Kaitan di antara data demografik dan faktor prognostik kepada kadar jangka hayat/ status akhir pesakit di analisis dengan Cox Regression. Lengkungan kadar jangka hayat dianalisa dengan menggunakan kaedah Kaplan Miere dan dibandingkan dengan test Log Rank.

Keputusan

Terdapat seramai 51 orang kanak-kanak yang dikenal pasti mengidap penyakit Tumor Keluarga Ewing (EFT) Hospital USM. Bagaimanapun hanya 29 kanak-kanak di masukkan ke dalam kajian kami setelah memenuhi kriteria kemasukan.

Purata jangkamasa temujanji adalah 21 bulan. Kadar jangka hayat menyeluruh(OS) untuk 1, 2, 3 dan 5 tahun adalah 62.1%, 44.8%, 30.2% dan 21.6% masing-masing. Kadar jangka hayat tanpa kejadian(EFS) untuk 1, 2, 3 dan 5 tahun adalah masing-masing 41.9%, 26.7%, 17.8% dan 0%.

Analisa Multivariate Cox Regression menunjukkan bahawa faktor pembedahan (p=0.030) dan faktor komplikasi (p=0.045), merupakan faktor prognostik yang signifikan terhadap kadar jangka hayat di kalangan EFT.

Kesimpulan

Kadar jangka hayat dikalangan masyarakat kita adalah setanding dengan negara-negara membangun yang lain. Walaubagaimanapun, kita masih jauh ketinggalan jika dibandingkan dengan negara-negara maju disebabkan kadar jangka hayat kita cuma menghampiri separuh daripada kadar jangka hayat mereka. Kami dapat mengenal pasti faktor pembedahan dan komplikasi merupakan faktor prognostik yang mempengaruhi kepada kadar peluang hidup pesakit EFT di kalangan pesakit kami.

ABSTRACT

Introduction

Ewing Family Tumor (EFT) is a very malignant and aggressive tumor. It was very rare tumor especially in Asia compare to western countries. During the past three decades, the prognosis of patient with EFT had improves considerably as shown in several clinical trials, mainly because of improved chemotherapy regimes. In our country, there is lack of reports in the treatment outcome and survival of children with EFT. There is no published study predicting the treatment outcome in Hospital USM at present.

Objectives

The objectives of this study were to evaluate the Overall Survival (OS) and Event Free Survival (EFS) rate of patients who were diagnosed with EFT. We want to evaluate the demographic data and identify the possible predictive factors that determine the EFS and OS rate of those children with EFT and treated in Hospital USM.

Methodology

This is a retrospective record review of children aged 0-18 years with EFT. Children were identified from registration data in Oncology Unit and medical records from Record Office HUSM. In case of uncontactable or deceased patients, a letter was sent to State Registry to obtain the end result/outcome of the patients. The associations of demographic and clinical factors with patients outcome were determined by Cox regression. Survival curves were estimated by the Kaplan-Meier method and compared by the Log-rank test.

Results

There were 51 patients identified from the registration but then only 29 children were enrolled in this study, which full filled all the inclusion criteria.

The mean duration follow up was 21 months. The OS rate at 1, 2, 3 and 5 years were 62.1%, 44.8%, 30.2% and 21.6% respectively. The EFS rate at 1, 2, 3 and 5 years were 41.9%, 26.7%, 17.8% and 0% respectively.

Multivariate Cox regression analysis showed that presence of surgical intervention ($p=0.030$) and major complications ($p=0.045$) were significant prognostic factors to the survival of EFT in this study.

Conclusion

Survival rate among our patients was comparable to other developing countries. However we are far away if compared to developed countries as the survival rate only achieved almost half from their survival rate. We are able to identify two significant independent prognostic factors to the survival for EFT in our patients which were surgical intervention and presence of major complications.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Hospital Universiti Sains Malaysia (HUSM) is the only tertiary centre for Paediatric Oncology in the East Coast of Penisular Malaysia, and is the referral centre for the childhood malignancies for the state of Kelantan, Terengganu and Pahang. The Paediatric Oncology Unit Hospital USM officially started in 1989. It is 23 bedded ward specifically designed for the treatment of children with oncological conditions. Most of the children are treated for haematologicaly malignancies which include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), lymphoma and multiple solid tumor as well as for bone tumor such as Osteosarcoma and Ewing Family Tumor. In Malaysia, only a few studies have been published on the outcome of Ewing Family Tumor (Lee A.C *et al.*2006).

1.2 EPIDEMIOLOGY AND INCIDENCE

Ewing Family tumor (EFT), are malignant small, round, blue cell tumors. In the past, Ewing's sarcoma (ES) was first described by James Ewing in 1921 as a "diffuse endothelioma of bone" (Ewing *et al.* 1921). They have also been identified as Ewing Sarcoma of soft tissue (extraosseous). In 1979, Askin *et al*., had described Askin tumor as part of EFT. In 1984, Jaffe *et al*., described PNET (Primitive Neuroectodermal Tumor) in Ewing Sarcoma. All together, they are classified as EFT as they share the same

histological, immunohistochemical and cytogenetic characteristics. It is the second most frequent primary bone tumor after osteosarcoma about 34% and 56% of the malignant bone tumors respectively. (National Cancer Institute, 2013).

The incidence varies among different racial group and it's much lower in the black population and in Eastern and South Eastern Asians. The incidence varies with age. In United States, Ewing Sarcoma is the most common in the second decade of life. The rate is 0.3 cases per million in children under 3 years of age and as high as 4.6 cases per million in adolescent age 15-19 years. It is a disease affecting children and young adults with a peak incidence at age 15 years. Cases are very rarely occur among African or Asian population.

Internationally the annual incidence rate is less than 2 cases per million children. The incidence of Ewing sarcoma has remained unchanged for the past 30 years. The incidence for all ages is one case per 1 million people in the United States. In patients between age 10 to 19 years, the incidence is between 9 and 10 cases per 1 million people. The same analysis suggests that the incidence of Ewing sarcoma in the United States is nine times greater in whites than in African Americans, with an intermediate incidence in Asians. Based on SEER, (Surveillance, Epidemiology and End Result) program series in the USA between 1973- 1985, this tumor rarely occur in black patients as only 3 black patients out of 650 cases of Ewing Sarcoma. (Ewing J *et al*.1972, Kowalewski A.A *et al*.2011).

It is more common in males compared to females with the ratio of 1.3 to 1.5: 1. Even though it's more common in children younger than 20 years old compared to elderly, it

tends to affect patients age more than 20 years old for the extraosseous subtype of EFT (Iwamoto Y, *et al.*2007).

1.3 ETIOLOGY

The exact etiology of Ewing Family Tumors is not fully understood. Some genes control when our cells grow, divide into new cells and die. *Oncogene* is the gene that helps cells to grow and divide. In the other way, *tumor suppressor gene* is a gene that controls cells division or make cells die. Cancers can happen by changes in the cell's DNA that turn on oncogene or turn off tumor suppressor gene. Researchers have found chromosome changes that lead to Ewing tumors, but these changes are not inherited. They develop in a single cell after a child is born. Nearly all Ewing tumor cells have changes that involve the *EWS* gene, which is found on chromosome 22. In most cases, there is translocation between chromosome 22 and 11. Occasionally, the translocation occurs between chromosome 22 and 21 and rarely between 22 and another chromosomes. The translocation causes the *EWS* gene to be activated and leads to overgrowth of the cells and development of this cancer, but the exact way that make the genes change is not yet clear. There are no known lifestyle-related or environmental that can cause Ewing tumors, therefore nothing can be done to prevent it from happening. The only known risk factors for Ewing tumors are age, gender, and race/ethnicity which can't be changed (American Cancer Society, 2016).

1.4 CLINICAL FEATURES

Ewing family tumor primarily occurs in the bone. The most common sites for Ewing Family Tumor are at the trunk and long bones. In truncal skeleton, the pelvis bone

predominates, followed by scapula, vertebral bones, ribs and clavicle. Among the long bones involved, the most common site is the femur and followed by humerus, tibia and radius/ulna. It has high tendencies to metastasize especially to the lungs, bone and bone marrow, while metastases to the lymph nodes are rare. The progression of the tumor is quite rapid to form large tumors within a few weeks. The commonest and earliest symptoms are pain followed by swelling. The pain can be intermittent and mild but progresses rapidly to very intense pain that requires analgesics. If the site of tumor is pelvic, it was associated with paraesthesia and limping gait. Other symptoms are non-specific such as fever, anemia, increased ESR, leukocytosis and an increase in Lactate Dehydrogenase (LDH) level (Iwamoto Y, *et al.* 2007).

1.5 DIAGNOSIS

The definitive diagnostic test is biopsy. It can be performed either by fine needle or core biopsy but preferably by incisional biopsy for an adequate sampling. Open biopsy is the best way to avoid violation of tissue flap planes and neovascular structure. Histologically, it composed of small round cells with high nuclear to cytoplasmic ratios that are arrayed in sheet. The cytoplasma is scanty, pale, vacoulated and characterized by faded boundaries. To differentiate EFT with other small round cell tumors are by cytogenetic and immunohistochemical studies, evidence that show translocation of t(11:22)(q24:q12) which is present in more than 85% of cases. Less occur, translocation involving EWS locus on chromosome 22 t(21:22)(q22:q12) and t(7;22)(p22;q12). In addition, it often PAS (Periodic Acid Schif) positive, (owing to intracellular glycogen) distinguished it from

lymphoma which is PAS- negative. Some of differentiated Ewing Sarcoma may exhibit neural differentiation; called as PNET. In 1979, Askin *et al*. described a small round cell tumor of thoracopulmonary region (Askin Tumor) that has different pathogenesis than Ewing Sarcoma/PNET but recent studies failed to demonstrate any significant differences in the outcomes. Recent studies revealed that pathognomonic translocation between the EWS gene on chromosome 22 and an ETS-type gene, most commonly Fli1 gene on chromosome 11 in more than 95% of Ewing Sarcoma, PNETs and Askin's tumor. Therefore, these lesions are grouped as the same entity called the Ewing's Family Tumor (EFT) (Iwamoto Y, *et al*.2007).

Other diagnostic tools that may help in term of diagnosis are imaging. Plain radiograph may exhibit periosteal reaction. It may present in any kind of bone tumor. Typically in Ewing Sarcoma, it appears ill defined, permeative or focally moth eaten, destructive intramedullary lesions in compared to sunburst type of periosteal reaction that found in osteosarcoma. The most precise imaging to see the local extent or degree of expansion is MRI. It helps for staging, surgical planning and to assess response to neoadjuvant chemotherapy or radiotherapy. In this study, the definitive diagnostic tools used were biopsy and HPE followed by serial's imaging either Ct scan or MRI to look for staging as well as to see respond towards the treatment. Bone scan also values in terms of to assess skip bone metastases. BMA (Bone Marrow Aspiration) also offered to see the extension into bone marrow (Iwamoto Y, *et al.*2007).

1.6 STAGING

The systems used for staging for both benign and malignant muskuloskeletal tumors are created by Ennecking, WF *et al.*1986. The systems are based on the histological grade of the tumor, local extend and the presence or absence of metastasis. It helps to guide surgical and adjuvant therapy. The stage of a Ewing tumor is one of the most important factors determining prognosis and in choosing the treatment. Many oncologist stage malignant bone tumor including Ewing Tumor that start in the bone according to AJCC (American Joint Committee on Cancer) systems, which is similar to Enneking's system. Extraosseous Ewing Tumor (Ewing Tumor that don't start in bone) are stage differently like other soft tissues sarcoma (American Joint Committee on Cancer Bone, 2010, American Cancer Society, 2016).

1.7 PROGNOSTIC FACTORS

The most unfavorable prognostic factor is the presence of distant metastasis at diagnosis. When the cancer had spread at the time of diagnosis, the 5 year survival rate is about 15%-30% compared with localized tumor which is around 70%. The prognosis is even worse in patients with bone marrow metastasis at the time of diagnosis (5-year Survival rate less than 20%) than those with isolated pulmonary metastasis (5-year Survival rate: 30%). In other words, the survival rate is slightly better if the cancer has only spread to the lungs as opposed to having reached other organs, (American Cancer Society, 2016). Previous studies have analyzed prognostic factors such as metastasis disease, age, the tumor size and the pelvic location are the poor prognostic factors (Bacci *et al*.,2000, Catterill *et al*.,2000,

Obata *et al*.,2007, Rodriguez-Gallindo *et al*.,2003) . Other unfavorable diagnosis includes larger size of tumor (> 200ml/8cm) and the site of tumor which is more central lesions as in the pelvis or spine in comparing to the other site such as on arms or legs. The age more than 10 years and poor response to chemotherapy also a poor prognostic factors, (American Cancer Society, 2016).

The histological grade has no prognostic significance because all Ewing sarcomas are considered high grade. Blood parameters such as elevated LDH, ESR, Total white and Anaemia indicates more extensive disease and poorer prognosis, (American Cancer Society, 2016).

Study done by Rodrıguez-Galindo *et al*.2007, revealed that older age, pelvic primary tumor, large tumors and metastatic disease were associated with worse outcome. However, only stage of disease and tumor size retained significance on a multivariate analysis.

The most important prognostic factors for patients with localized disease were the local extension and for patients with metastatic disease, the only prognostic indicator was the pattern of metastasis.

1.8 SURVIVAL

There are no single criteria for definition of Overall survival (OS) and Event Free survival (EFS). OS is defined as the time from the diagnosis until death from any causes or until last follow up. EFS is defined as the interval between the date of diagnosis and the earliest

occurrence of the following events: induction failure, relapse, death from any cause, last contact and development of a second malignancy. (NCI Dictionary of Cancer Terms)

In this study, EFS was considered as the time from diagnosis to the date of any event or to the date when patients were confirmed to be well, or at the date of census, whichever occurred first. The events were considered as relapsed, defaultation, death or any major complications.

OS was considered as the time from diagnosis to the date of death or at the date of census or last follow up.

The 5-year survival rate refers to the percentage of patients who live *at least 5 years* after their cancer is diagnosed. In developed countries, the 5 year relative survival for children with bone cancer improved from 49% in the period 1975-1984 to 63% in the period 1985-1994 for both Osteosarcoma and Ewing sarcoma. The survival rate for osteosarcoma was higher than those for Ewing's Sarcoma, (National Cancer Institute, 2013). During the past 3 decades, the prognosis of patients of EFT has improves considerably as shown in several clinical trials, mainly because of improved chemotherapy regimens, (Burgert *et al*.,1990, Grier *et al*.,2003, Jurgens *et al*.,1998, Nesbit *et al*.,1990, Paulussen *et al*.,2001).

1.9 TREATMENT

Treatments of Ewing Family Tumor include neoadjuvant therapy, surgical treatment and chemotherapy to treat distant metastasis regardless of initial staging. Before the use of multi- agent chemotherapy, the long term survival was less than 10% which improved

trendenmously to up to 70% after introduction of chemotherapy. Current anti- cancer drugs proven to be effective are doxorubicin(DXR), Vincristine(VCR), Cyclophosphamide(CPM), Actinomycin-D(ACT), Ifosfamide(IFM) and Etoposide(VP16), (Iwamoto Y *et al*.2007).

In 1962, Pinkel *et al.,* reported first using cyclophosphamide in solid tumor including EFT and showed regression of pulmonary metastasis and pleural effusion. In 1968, Hustu *et al.* reported using the combination of cyclophosphamide, VCR and radiotherapy resulted in sustained respond in 5 patients with Ewing's sarcoma. This is the starting of the modern multimodality in the treatment of Ewing Sarcoma.

The multi agent treatments evolved further as in 1974, Rosen *et al* used the combination of 4- drugs regime consist of VACD regime, (VCR, ACT, CPM and DXR) plus radiotherapy. This combination resulted in improved long term survival of 12 patients with Ewing sarcoma. Long term follow up of the IESS-1 study (Intergrouped Ewing's Sarcoma Study) had demonstrates the superiority of VACD regime (EFS: 60%) compare to 3 drugs regime (VAC Regime-EFS 24%). In Europe, the effect of VACD four drugs regimen was also investigated in CESS-81(Cooperative Ewing's Sarcoma Study), revealed that 5-year free survival of non- metastasis Ewing sarcoma was 55%. In CESS-86 study, Ifosphamide (IFM) was added in VAC regime in the treatment of large tumor instead of DXR and VAC regime for a smaller tumor size. The 10-year survival rate was 52% in IFM group compared to 51% in DXR group suggesting the usefulness of VAC plus IFM as well as VAC plus DXR in the treatment of Ewing Sarcoma, (Iwamoto *et al*.,2007).

Local treatments have a role in the management of EFT which included surgical treatment as well as irradiation but it remains controversial. Previous reports has demonstrate reduction rate of recurrence with wide resection up to less than 10% for local control to those tumor which surgery is applicable and it should be made on an individual basis. Ewing sarcomas are sensitive to both chemotherapy and irradiation. The standard treatments for resectable tumor, begin with neoadjuvant chemotherapy, followed by limb-salvage and post adjuvant chemotherapy. Formerly amputation was the only surgical method for local control. Currently limb salvages procedures include local resection and reconstruction had been replaced.

1.10 MANAGEMENT IN HUSM

In Hospital USM, paediatric oncology ward (6 Utara) in collaboration with 2 Selatan (adult oncology ward) and Orthopaedic ward (4 Selatan) are the team that involved in the management of oncology cases including EFT patients. Ward 6 Utara managed younger age patients up to 12 years old while patients above 12 years were managed by oncology adult in terms of chemotherapy and radiotherapy. Resectable tumors were referred to Orthopaedic surgeons for excision.

All children who were suspected to have bone tumor based on the initial imaging either CT scan or MRI were proceed by gold standard diagnostic tool which were biopsy and HPE to confirm the diagnosis. Prior to chemotherapy, most of the children were referred for central line, either chemoport or Hickman catheter under general anaesthesia for prolonged chemotherapy medications usage and regular blood taking for monitoring the disease

progression and complication. Bone marrow aspiration (BMA) was done at the time of diagnosis to look for metastases to bone marrow. Imaging with CT scan or MRI was done to stage the disease and predict the prognosis for the patients.

Any patients with resectable tumor were started on neoadjuvant chemotherapy followed by surgical resection and then post adjuvant chemotherapy. Then, the patients were undergone serials imaging consist of MRI/CT scan thorax as well as bone scan to stage the disease, assess the respond to the treatments, looks for recurrence and site of metastasis.

In 6 Utara, the common chemotherapy protocol regime that had been used for the past 10 years in the management of Ewing Family Tumor includes Euro Ewing 99 protocol and PNET protocol.

While in 2S (adult oncology unit), the protocol that had been used was CAV/IE (Cylophosphamide, Actinomycin, Vincristine/ Ifosphamide, Etoposide) regime.

Others chemotherapy regime that had been used included Modified PNET protocol and MSK protocol.

Those who showed poor respond to the current treatments were offered for second line chemotherapy which was ICE protocol. To those who were at the end stage with overwhelming metastasis were counseled and offered for palliative care.

Others treatments included supportive care especially during chemotherapy. For children that developed severe neutropenia will be given neutropenic regime and treat infections with antibiotic if they developed infection/sepsis as a consequences of severe neutropenia.

Supportive blood transfusion would be given if they developed anaemia especially when patients undergone certain procedure or while on chemotherapy.

The patients who were having sepsis as consequences of severe neutopenia were commenced empirical broad spectrum antibiotic while awaiting culture and sensitivity and the choices were according to our local sensitivity or resistant pattern data from microbiology lab. Then it was change accordingly to the sensitivity based on the blood culture result. Antifungal was added if indicated. Others supportive measures such as inotropic support, mechanical ventilator, total parenteral nutrition were also available. Patients who economically compromised were referred to social welfare for financial support.

1.11 FOLLOW UP

All patients were followed up from time to time at paediatric clinic as well as orthopaedic clinic, Hospital USM. They were seen more frequently in the first year. If they were doing well, the follow up is every 6 months until adulthood. During follow up, assessment was towards looking for remission status, any recurrence or any secondary complication that might arise. It's included thorough physical examination, blood investigation including infectious screening as well as serial imaging such as CT scan/MRI.

CHAPTER TWO

OBJECTIVES AND HYPOTHESIS

2.1 Objectives

General objectives

To determine the survival rate and prognostic factors of Ewing Family Tumor (EFT) children receiving treatment in Hospital USM from 1st January 2002 to 31st December 2012.

Specific objectives:

i. To describe the demographic and clinical characteristic of EFT children in Hospital USM.
ii. To determine Overall and Event Free Survival rate of Ewing Family Tumor (EFT) in Hospital USM.
iii. To describe the prognostic factors for Overall survival in EFT children treated in Hospital USM.

2.2 Hypothesis

1) The Overall and EFS of EFT children treated in Hospital USM is comparable to other developing countries.

2) The prognostic factors for survival in children with EFT in Hospital USM are age at diagnosis, gender, non-pelvic tumor, disease profile, status of metastasis at diagnosis, the size of the tumor, surgical intervention, lung metastasis at diagnosis, skip bone metastasis, chemotherapy regime and major complications.

CHAPTER THREE

METHODOLOGY

3.1 Study area and patients

This study was conducted in Hospital Universiti Sains Malaysia (USM), Kubang Kerian Kelantan. Paediatric Oncology Unit Hospital USM officially functioned in 1989. It is the only tertiary centre for Paediatric Oncology in East Coast of Penisular Malaysia. The ward involved included ward 6 Utara (Paediatric Oncology) for children age 12 years and below. Ward 6 Utara consists of 23 beds mainly for oncology patients. While for patients above 12 years old, they were placed in adult oncology ward at 2 Selatan. Since this study involved children age up to 18 years old, both 6 Utara and 2 Selatan ward were involved.

All children who were diagnosed to have Ewing Family Tumor (EFT) between 1st January 2002 - 31st December 2012 at Hospital USM with additional follow up within 12 months were included in the study. Age between 0-18 years old at diagnosis and the diagnosis of EFT based on Histopathology Examination (HPE) findings that fulfilled the criteria of ICD10 –C41.9 for Ewing Family Tumor. Children who were unable to trace outcome, transferred to another hospital for continuation of treatment, as well as referred from other hospital for continuation of chemotherapy and those with missing data were excluded.

Most of the children were from Kelantan, Pahang, Terengganu and Kedah. Some of

them were from other parts of states in Malaysia such as Johor and Kuala Lumpur. In between the chemotherapy, some of them received supportive treatment in the hospital nearby their hometown.

3.2 Treatment protocols

Children with EFT who were diagnosed from 2002-2012, were treated with Euro Ewing 99 Protocol for paediatric oncology unit in 6 Utara, while in 2 Selatan they were treated with CAV/IE protocol. Some of the patients used PNET protocol or Memorial Sloan Kettering (MSK) protocol. While for salvage and palliative chemotherapy, ICE protocol was used as chemotherapy regime.

3.3 Study Design

This study was a retrospective record review study. The name and registration numbers were obtained from registration data at paediatric oncology unit, orthopedic ward and record office Hospital USM. Code number was given to each patient with a separate list of name. Registered number were recorded in separate list and kept by researcher. Data were entered using code number. Total of 51 cases were available from the registration record but only 46 case notes were traceable. Out of 51, 20 of them were excluded. 15 of them due to final diagnosis not full filled the criteria of HPE diagnosis of EFT and 5 of them due to missing folder. One patient was started chemotherapy at other hospital and continued chemotherapy at our hospital. One of them was diagnosed earlier than study period. Total of 29 patients were enrolled in this study. All the traceable case notes were reviewed and the data were collected on a standardized case recording form (*Appendix A*).

The status of metastasis/ localised at diagnosis was taken based on the first staging imaging done after confirmation of diagnosis by biopsy and HPE. Skip bone metastasis was identified by first bone scan done. The size of tumor was estimated by CT scan/MRI done at diagnosis and the largest diameter was used. The chemotherapy regime data taken in this study were the first chemotherapy given to the patients.

3.4 Consent and ethical approval

All parents were contacted via phone or approached during their regular follow up in oncology clinic but most of them were contacted via phone. A waiver of consent for parents whose children already passed away or not contactable (after attempted to contact them) was approved by USM Research and Ethical Committee (*Appendix D*). Some of them were un-contactable or deceased. Therefore a letter was sent to State Registry. The status and the cause of death were obtained from the information given by State Registry, (*Appendix E*).

3.5 Sample size

Sample size was calculated using Power and sample size calculation software (version 3.0, January 2009). Sample size calculated, with type 1 error of 0.05 and power (1-B) of 0.8, M1 were estimated median survival time based on previous study by Kai *et al.,*2012. With HR 2.5, accrual time: 120 months, additional follow up: 12 months with m1 of 19 months, a sample size with 10% drops, 52 cases is required.

While the other study by Kutlut *et al.*2004, HR: 3, accrual time 120 months, additional follow up 12 months, m1 of 20 months, a sample size with 10% drops, 93 cases are required. However because of study limitation only 51 patient's record were identified

during the time of study, there was no sampling method applied. All 51 cases were enrolled in the study.

3.6 Outcomes Measures

The outcomes were the EFS and OS. On top of that the prognostic factors and the demographic data which affected the OS and EFS were identified. OS was calculated from the time of diagnosis to death or till the last contact or date of census. EFS was measured from time of diagnosis to the date of any event, well/cure or at date of census, which ever occurred first. Events were considered as defaultation, death, major complications (neurology complications, cardiac complications, neutropenia sepsis, bleeding complication, secondary malignancy, treatment complications) or relapsed.

3.7 Statistical Analysis

The statistical analysis was performed using software SPSS version 19. Descriptive data was analysed. The numerical data was checked for normal distribution by using histiogram, skewness, kurtosis, and boxplot diagram. As it was normally distributed, the result were expressed in mean (SD). The rest of the data were expressed in number and percentage (n, %).

Event Free Survival, Overall survival and median survival rate were described using Kaplan Meier method. Log rank test was used to compare the survival curves of the subgroups.

Univariate Cox proportional hazard model was used to explore predictors. Several variables were examined as potential predictors for OS. These variables included

gender, age at diagnosis, size of tumor (cm), pelvic vs non-pelvic site of tumor, lung metastasis, skip bone metastasis, disease profile, chemotherapy regime, surgical intervention and complications. The factors with p value less than 0.25 were included in the multivariate Cox proportional hazard. Those variables with more than 2 group to compare were used multiple comparison with bonferoni corrected p value. P value < 0.05 was considered as significant. The variables in the final model were examined for interaction and assumption.

3.8 Definitions

Remission: absence of the disease clinically and radiologically.

Defaultment: define as absence from scheduled therapy or follow up more than 4 weeks.

Overall survival: from the date of diagnosis till patients death/ last contact/ date of census.

Event free survival: is time from diagnosis to the date of any event, date when patients confirm to be well/cure, or to the date of any major complications.

Median survival: is the time when half of children are expected to be alive (the chance of surviving beyond that time is 50%)

Relapsed: any disease recur

Major Complications: Includes severe sepsis, Neurological complications, Cardiology complications, Coagulations and bleeding, Complication treatments (DVT, liver toxicity) secondary malignancies. The complication excluded death as death was considered the outcomes.

Events: Were considered as well/cure, defaultation, death, major complications, date of census.

CHAPTER FOUR

RESULTS

Total number of 51 children who were suspected with Ewing Family Tumor (EFT) at presentation, were seen in Paediatric Oncology ward and Orthopaedic Ward from 1st January 2002 to 31st December 2012. These data were obtained from the registration record office. The patients involved only included paediatric patients aged 0- 18 years of age.

Out of 51 patients, only 29 patients were enrolled in the study. This is because 15 of them were diagnosed of other diagnosis based on biopsy and HPE (Histopathology examination). The diagnosis include Chronic Osteomyelitis (n=6), Osteosarcoma (n=5) and Langerhans Cell Histiocytosis (n=1). Two patients have normal HPE result and one patient with uncertain diagnosis due to missed follow up.

Thirty one patients with confirmed EFT but two of them need to be excluded because one of them was started chemotherapy at other hospital and used different chemotherapy regime than our hospital. The other one was diagnosed earlier than our study period (2000). Five folders were missing.

4.1 Demographic Profile of Children with Ewing Family Tumor

Table 1: Demographic profile of children with Ewing Family Tumor (EFT).(n=29)

Features	n	%
Gender		
Male	16	55.2
Female	13	44.8
Age		
<10 years	6	20.7
≥10 -18 years	23	79.3
Race		
Malay	25	86.2
Chinese	1	3.4
Indian	3	10.3
Parental Education		
Primary	7	24.1
Secondary	7	24.1
Tertiary	5	17.2
Missing data	10	34.5

Table 1 above showed demographic profile of children with Ewing Family Tumor in HUSM from 2002-2012. Out of 29 subjects, the minimum age was 4.6 years and the maximum age was 17.7 years. Mean age was 12.0 years old (SD: 3.74). Majority of patients were 10 years and above (79.3%).

Most of patients were predominantly male (55.2%) compare to female (44.8%). The incidence in male was 1.3 times higher compared to female. Majority were Malays (86.2%). Whereby, others were from Indian (10.3%) and Chinese (3.4%).

In terms of academic background of parent, one third of data was missing, (n=10, 36.7 %) as no documentation of the parental education in the folder. Otherwise it was nearly well distributed among primary (24.1%), secondary (24.1%) and tertiary (17.2%) level of education.

4.2 Patients Characteristic of Ewing Family Tumor

Table 2: Patients Characteristic of Ewing Family Tumor (n=29)

Characteristic	n	%
Primary Tumor site		
Extremities	16	55.2
Pelvis	8	27.6
Axial	5	17.2
Disease Profile		
Classical Ewing Sarcoma	11	37.9
PNET	16	55.2
Extraosseous	2	6.9
Symptoms		
Pain	2	6.9
Palpable mass	8	27.6
Pain and mass	10	34.5
Paraplegia	8	27.6
Paraesthesia/redness	1	3.4
Size of tumor		
<8cm	3	10.3
≥8cm	21	72.4
Missing data	5	17.2
Metastasis at diagnosis		
Yes	11	37.9
No	15	51.7
Missing data	3	10.3

Characteristic	n	%
Lung metastasis at diagnosis		
Yes	11	37.9
No	15	51.7
Missing data	3	1
Skip bone metastasis at diagnosis		
Yes	3	10.3
No	16	55.2
Missing data	10	34.5
Surgical intervention		
Surgery	13	44.8
No surgery	16	55.2
Chemotherapy protocol		
Ewing Euro 99	8	27.6
PNET[1]	3	10.3
CAV/IE[2]	14	48.3
MSK[3]	2	6.9
Unknown	1	3.9
Complications		
Sepsis	8	27.6
Neurology complication	3	10.3
Others[4]	3	10.3
Nil	15	51.7