EVALUATION OF PROGNOSTIC FACTORS AND SURVIVAL OF PATIENTS WITH METASTATIC BONE DISEASE

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UNIVERSITI SAINS MALAYSIA

2016

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by

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Dissertation submitted in partial fulfillment of the requirements for the Degree of Master of Medicine (Orthopaedics)

May 2016

ACKNOWLEDGEMENT

In the name of Allah the most passionate and the most merciful

First of all, alhamdo Lellah at the beginning and forever. I am grateful to the Allah, Glory to Him and the Exalted for the good health and wellbeing that were necessary to complete this dissertation.

I wish to place on record my sincere and heartfelt thanks to my main supervisor ***Professor Dr. Wan Faisham Nu'man Wan Ismail*** *for providing me with all the necessary guidance, enthusiasm, advices, friendship, and moral support during all stages of this research. I express my grateful to my head of department* ***Professor Dr. Mohd Imran Yusof*** *and, extremely thankful and indebted to him for sharing expertise, sincere, valuable guidance and encouragement extended to me. I would also like to thank* ***Assoc. Prof. (Madya) Dr. Abdul Halim Yusof*** *for his encouragement, support, advices and wise suggestions throughout the study.*

My special words of thanks to all ***specialist in orthopedic department*** *for their sincere help, constant support and friendly advices which it was very beneficial in my study.*

I wish to express my immense gratitude to ***Dr. Kamarul Imran*** *for his valuable scholarly suggestions and kind cooperation during various stages of this work.*

I wish to record my heartfelt Homage to my father ***Faissal Abumarzouq****, who encouraged me in all my endeavors at all stages of my life and career, to my* ***Mother***

Nathmia Abumarzouq *and* ***Sisters*** *for their affection, care, moral support and understanding shown during my study time.*

I express my deep sense of gratitude to my dear wife ***UST. Mona Abumarzouq****, for inspiring me during my study and her unlimited consideration, patiently and helpfulness extended to me to complete this work.*

I am highly thankful to ***Yayasan Khazanah family staff particularly, En. Kamarul Bahrein Sharif, Ms. Intan Zalila Mohd Yusof, Ms. Emilia Maizura Harun, Ms. Raja Nor Dianna Binti Raja Harun, Ms. Norhidayah Aslah****, for their financial support; As they provided me with a complete scholarship and in between they allow me to attend leadership programs, and many related orthopedic conferences and workshops and so many thing which I can't count here; but without* ***Yayasan Khazana*** *difficult I can carry out with my study as perfect as it is currently.*

My sincere thanks go to all ***my friends*** *for being there and supporting me with friendly advice, cups of tea and random conversations particularly,* ***Dr. Abdelrahman Zeuter, Dr. Hssan Azeez, Dr. Khalid Hajissa, and Dr. Munvar Shaik*** *who have been great friends.*

Last but not least I would also like to acknowledge the ***faculty of medical sciences****,* ***record office staff*** *for their help and support.*

DR. Mahmoud Faissal Refa'at Abumarzouq

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

CAMs	cell adhesion molecules
CNB	Core needle biopsy
Ct	Computer tomography
ECOG	Easter Cooperative Oncology Group
FNA	Fine-needle aspiration
HUSM	Hospital University Sains Malaysia
IL-6	Interleukin 6
MMPs	Metalloproteinases
MRI	Magnetic resonance imaging
MSTSS	Musculoskeletal Tumor Society Score
PS	Performance status
PTHrP	parathyroid hormone related protein
QOL	quality of life
RANKL	Receptor activator of nuclear factor-kB ligand
SPSS	Statistical Package for Social Scientists
SRE	Skeletal-related events
THR	Total Hip Replacement

PENILAIAN FAKTOR RAMALAN DAN KADAR KELANGSUNGAN HIDUP PADA PESAKIT DENGAN PENYAKIT TULANG METASTATIK

ABSTRAK

PENGENALAN

Pengurusan penyakit tulang metastatik masih mencabar, bersama-sama dengan peningkatan dalam menguruskan tumor pepejal utama, pesakit hidup lebih lama dan mereka berpotensi untuk mendapat metastatik kepada tulang lebih daripada mereka ada sebelum ini. Pelbagai pilihan rawatan mungkin boleh diberi kepada pesakit termasuk rawatan perubatan, radiasi, kemoterapi dan pembedahan. Pembedahan untuk penyakit tulang metastatik memberikan keputusan yang memuaskan, bagaimanapun terdapat beberapa faktor yang mempengaruhi kelangsungan hidup pesakit yang mempunyai penyakit tulang metastatik seperti status prestasi, jenis tumor utama, defisit neurologi, tulang patologi, metastasis kepada organ viseral dan akhir sekali adalah kemoterapi. Oleh itu kajian ini dijalankan untuk menilai faktor-faktor ramalan yang menjejaskan kelangsungan hidup dan kualiti hidup pesakit.

KAEDAH

Seramai 40 pesakit yang mempunyai penyakit tulang metastatik dirawat segara pembedahan antara tahun 2008 sehingga tahun 2015 di unit onkologi ortopedik, Hospital Universiti Sains Malaysia, mereka telah dinilai secara retrospektif untuk menilai faktor-faktor ramalan yang menjejaskan kelangsungan hidup, manakala borang soal selidik status prestasi ECOG (Eastern Cooperative Oncology Group) telah digunakan untuk menilai kualiti hidup pesakit pada tiga, enam dan dua belas bulan selepas pembedahan. Selepas itu, kelangsungan hidup dianalisis dengan kaedah Kaplan- Meier.

KEPUTUSAN

Terdapat 29 wanita dan 11 lelaki, tumor utama yang paling kerap adalah kanser payudara dengan 42.5%, diikuti oleh kanser tiroid 17.5%. pesakit selamat14 (37.8%), manakala 23 (62,16%) pesakit meninggal dunia, dan kelangsungan hidup pertangahan ialah 36 bulan. Min umur pada adalah 54,43 tahun, terdapat 30% (12/40) melebihi 60 tahun dan 70% (28/40) di bawah 60 tahun, berdasarkan kumpulan umur, kadar kelangsungan hidup adalah ketara secara statistik dengan nilai p (0.028). Faktor-faktor ramalan lain adalah termasuk kemoterapi dan lokasi metastasis tulang (appendicular, tulang paksi atau kedua-duanya) juga didapati mempunyai hubungan yang signifikan dengan nilai hidup p (0.003, 0.021) masing-masing. Jenis pembedahan juga dilihat sebagai faktor penting yang berkaitan dengan kadar kelangsungan hidup (p nilai 0,038), pembedahan reseksi dan endoprosthesis adalah prosedur yang kerap dilakukan di pusat kami untuk (pinggul, tulang paha proksimal, bahu dan kecederaan sekitar sendi lutut) 58.97% (n = 24), diikuti oleh prosedur Harrington untuk pelvik yang merupakan 17.95%.

Status prestasi ECOG (0-2) dan ECOG (3-5) pesakit telah dinilai dan didapati signifikan secara statistik sebagai faktor ramalan untuk kelangsungan hidup dalam kedua-dua kumpulan selepas tiga bulan, enam bulan dan dua belas bulan pembedahan.

KESIMPULAN Kesimpulannya faktor ramalan yang memberi kesan siginfikan kepada kelangsungan hidup pesakit dengan penyakit metastasis tulang adalah umur kurang daripada 60, lokasi kecederaan tulang, rawatan kemoterapi sebelumnya, dan jenis prosedur pembedahan yang dilakukan. Tambahan lagi kajian ini menunjukkan bahawa kualiti hidup adalah signifikan secara statistik berhubung dengan jenis pembedahan dan kelangsungan hidup secara keseluruhannya

EVALUATION OF PROGNOSTIC FACTORS AND SURVIVAL OF PATIENTS WITH METASTATIC BONE DISEASE

ABSTRACT

INTRODUCTION

Management of metastatic bone disease is still challenging, along with the improvement in managing primary solid tumors, patients survive longer and they become potential to have metastatic lesions of bone more than they had before. A variety of treatment options could possibly be given to those patients includes medical treatment, radiation, chemotherapy and surgical intervention. The surgical intervention for metastatic bone lesions gives satisfactory outcome. However, there are few factors affecting the survival of patients with metastatic bone disease such as performance status, type of primary tumor, neurology deficit, pathologic fracture, visceral organ metastasis and chemotherapy administration. This study was conducted to evaluate the prognostic factors affecting the median survival and patient's quality of life.

METHODS

A total of 40 patients with metastatic bone disease treated surgically between 2008 to 2015 at orthopedics oncology unit, Hospital Universiti Sains Malaysia were evaluated retrospectively, for survival prognostic factors, while the performance status questionnaire of ECOG (Eastern Cooperative Oncology Group) was used to assess the patient's quality of life at three, six and twelve month after the surgery. Subsequently, survival rate was analyzed by the Kaplan-Meier method.

RESULTS

There were 29 female and 11 male, the most common primary tumor was breast cancer with 42.5%, followed by thyroid cancer 17.5%. Over all 14 (37.8%) patients survived, while 23(62.16%) patients died, and the median survival was 36 months. Mean age at presentation was 54.43 years, and there were 30% (12/40) above 60 years and 70% (28/40) below 60 years. Based on the age groups, the survival rate was statistically significant p value (0.028). Other prognostic factors include chemotherapy administration and site of bone metastasis (appendicular, axial bone or both together) were also significantly correlated with the survival p value of (0.003, 0.021), respectively. Types of the surgery was a significant factor associated with the survival (p-value 0.038), resection and endoprosthesis surgery was the most procedure performed in our center for (hip, proximal femur, shoulder and around knee joint lesions) 58.97% (n=24), followed by Harrington procedure for pelvic involvement which was 17.95% . Performance status ECG (0-2) and ECOG (3-5) of patients was evaluated and found to be statistically significant as a prognostic factor for survival.

CONCLUSION

In conclusion, the prognostic factors that significantly affect the survival of patient with bone metastasis were age which was less than 60, location of bone lesions, previous chemotherapy, and the type of performed surgical procedure. Additionally, the study revealed that the quality of life significantly correlated with the types of surgery and overall survival. Furthermore, the performance status (ECOG) significantly correlated with the types of surgery and age.

CHAPTER 1

INTRODUCTION

1.1 Cancer and bone metastases in Malaysia

In Malaysia, a total of 18,219 new cancer cases in 2007 were diagnosed and registered at the National Cancer Registry. It comprises of 8,123 (44.6%) males and 10,096 (55.4%) females. The most common cancers among population of Malaysia is breast (18.1%) followed by colorectal (12.3%), lung (10.2%), nasopharynx (5.2%), cervix (4.6%), lymphoma (4.3), leukaemia (4.1), ovary (3.6), stomach (3.5) and liver (Kachnic *et al.*). This was reported by (Adler and Gill) in Malaysia reports in 2007 (Figure 1:1).

Staging was reported for 8,869 from 18,219 (48.7%), stage I was found to be 17.0%, whereas 25.3% stage II, stage III and stage IV 25.0%, 32.7% respectively . Therefore, at the time of diagnosis, 57.6% were already at advance stages of cancer (Lim and Azura, 2008).

Breast cancer was the most common cancer in females and it was the most common cancer among population regardless of sex in Malaysia, Colorectal cancer was the second most common cancer after breast cancer and second most common cancer in males and females in Malaysia. Lung cancer is the most common cancer among males and third most common cancer in the general population.

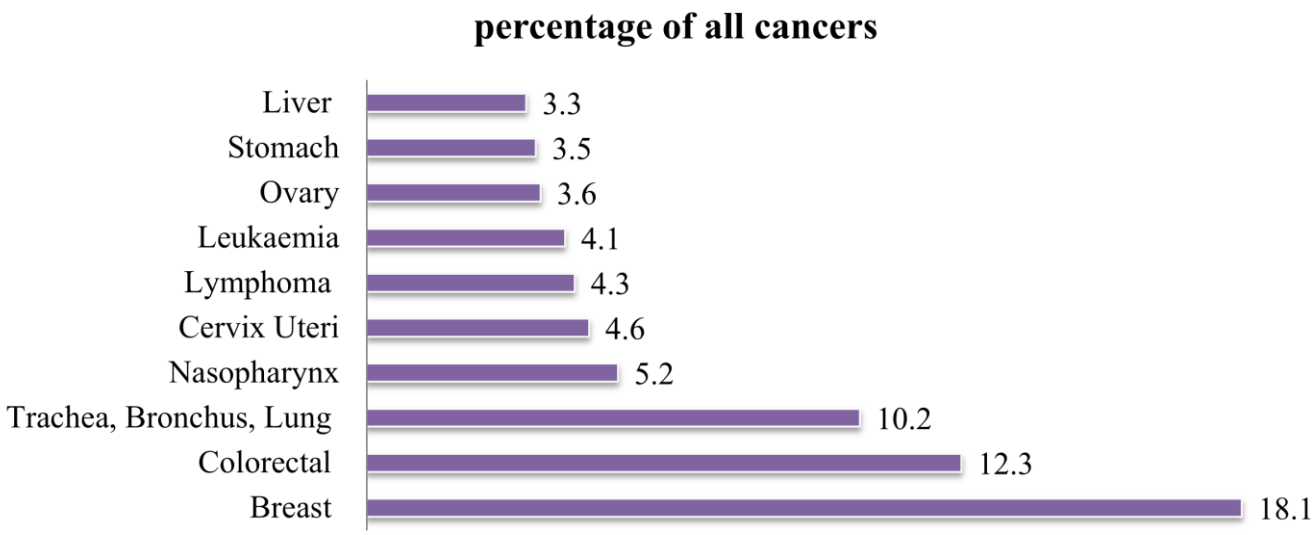

Figure 1:1 The prevalence of the most common cancers reported among Malaysian population regardless of age sex and race, reported in Malaysian (NCR) 2007.

There were 502 new prostate cancer cases diagnosed in 2007 which was reported in NCR, with prostate cancer considered the fourth most common cancer in Malaysia among males. The incidence of prostate cancer increases after the age of 45 years and higher in Chinese males followed by Malay and Indian.

1.2 Metastatic bone disease

Metastases to Bone from carcinomas are considered a medical, social and economic issue. About one-half of all primary cancers tend to disseminate to the bone, which is the third most frequent site of metastatic spread after the lung and the liver. Epidemiological investigation has shown that of 1.2 million new cases of cancer each year in the USA, in which about 300 000 will eventually develop a bone metastasis (Hage *et al.*, 2000). Tumors which have a predilection to dissemination to the bone are prostate (32%), breast (22%) and kidney (16%) followed by the lung and the thyroid, the spine, pelvis, ribs, skull and proximal long bones; those are the sites most commonly involved (Bauer, 2005; Toma *et al.*, 2007). In metastatic bone disease, six month survival rates have been reported in patients with primary solid tumor prostate cancer, breast cancer, lung cancer and kidney (98% ,89% ,50% 51%) respectively.

1.3 Justification of the study

1.3.1 Morbidities caused by Metastasis to the Bone

Most patients with metastatic bone disease have severe bone pain and debility. Moreover, they are sometimes bed bounded due to pain. Bone pain is frequently the first sign of metastatic disease and approximately 80% of all breast cancer patients will have one episode of bone pain that requires treatment. A major cause of prolonged disability is pathologic fracture (eg, rib fracture, long bone fracture and vertebral collapse), which is the second most common complication of bone metastases, occurring in 10% to 20% of patients. Hypercalcemia of malignancy developed in approximately 10% to 15% of patients; where elevated serum calcium levels from bone destruction can lead to gastrointestinal, renal, and central nervous system dysfunction. Spinal cord compression occurs in up to 5% of patients with metastatic bone disease (Coleman *et al.*, 2010).

Skeletal-related events (SRE) cause significant morbidity reduced performance status, quality of life (QOL), poor functional capacity and reduced survival.

The economic consequences of metastatic bone disease are substantial. In a retrospective analysis of breast cancer patients with bone metastases, the cost of treating skeletal complications was approximately $52,000 and more in patients with skeletal-related events than in patients without these events. There is also an estimated cost of 1.9 billion dollars every year in the United States, cost of treatment of a single SRE episode per patient varying from USD 6,973 to 11,979 (Jayasekera *et al.*, 2014).

Despite of various studies being done on prognostic factors of metastatic bone disease, no concrete conclusions at this time available.

The effect of surgical treatment on the function and the survival of patients with metastatic bone disease

Metastatic bone lesions do not always require surgical intervention; factors influencing the decision include size, location of the particular lesion, general medical status and expected survival of the patient. A small metastatic lesion that affects <50% of the cortex or a lesion in a non-weight-bearing bone (e.g. fibula bone) may not require surgical intervention, patients with severe medical comorbidities or a short expected remaining survival time may not be good candidates for surgical intervention, and some lytic lesions in the extremities were not at risk for pathological fracture might be treated with radiation and medications.

However, non-operative management is rarely utilized for pathologic fractures in the lower extremity due to metastatic bone lesion, but in certain cases such as patients with severe comorbidities such as cardiopulmonary disease or widespread metastasis with a short expected remaining life span (less than four weeks) may not tolerate surgery.

Local control of the metastatic lesion can be achieved by either wide resection and reconstruction or intralesional curettage with an adjuvant modality as this can improve survival compared to those patients with no surgical intervention done, with no survival difference (Weber *et al.*, 2006), Unique factors in our setting compared to western communities are that many patients before coming to see professionals they tend to use deferent types of alternative treatment, causing

delayed presentation. So by doing this study, we hope to be able to evaluate whether this factors will influence the outcome of surgical treatment.(Katagiri, 2014).

CHAPTER 2

LITERATURE REVIEW

2.1 Characteristic of bone metastasis

The bone of patients with breast cancer is the first site to be affected in 26% of cases and 74% of all patients. As the lesions may be osteolytic, osteoblastic or mixed; the five-year survival rate for metastatic breast cancer is 22%. Lung cancer 'Small-cell' carcinoma and adenocarcinoma frequently had metastasis to the skeleton; the lesions are usually osteolytic and only in 25% of the cases are osteoblastic (table 2:1). Lung cancer has with bone involvement prognosis not promising as the five-year survival rate only 2%, the 'non-small-cell' type of bronchogenic carcinoma has a five-year survival rate reach to 10% after surgery. Furthermore, the prognosis after irradiation is 3% to 9%, and 14% after local irradiation plus chemotherapy. However, the 'small-cell' type has a worse prognosis, and it is usually treated by chemotherapy with or without radiotherapy with a disease-free survival at two years in only 17% of cases (Fairchild, 2014).

Spine lesions are the most common site of bone involvement in patients with prostate cancer, followed by femur, pelvis, ribs, sternum, skull, and humerus. Symptomatic lumbar and cervical metastases involvement develop in 27% and 6% of prostate patients. The lesions are usually osteoblastic (84%) or mixed (12%) and rarely osteolytic (4%). pathological fractures are rarely seen in patients with spine metastasis due to prostate cancer that is referred to Osteoblastic nature of the lesions. Moreover, a high potential for union after fixation and five-year survival rate for metastatic prostate cancer is around 33%(Sarahrudi *et al.*, 2009).

Kidney cancer has the potential to develop lung metastasis followed by skeletal and brain. In cases of bone lesions, the cortex may disappear without periosteal reaction and soft-tissue expansion, with high risk of pathological fracture in around (50%) of cases that especially in spine involvement as well as long bones. Metastases from renal cancer originally known to have intense vascularity because of that selective embolization which is indicated preoperatively to reduce bleeding during operation especially for lesions located in the spine, pelvis or shoulder girdle, in which five-year survival rate after resection of a solitary metastasis 35% is expected. On the other hand, multiple lesions and palliative surgery indicated the median survival of about 12 months.

In thyroid cancer, patients develop bone metastasis in 4%, pulmonary metastases in 9% of cases, bone metastases are usually osteolytic and hypervascularised. Solitary lesion may be observed in 30%, rate of survival at five years is 44%. However, the expected survival is less than one year for anaplastic tumors(Sim, 1988).

Table 2:1 Incidence and Prognosis of Bone Metastases due to variation of primary tumor

	Incidence of advanced disease	Median survival in months	5-yr survival
Myeloma	95-100%	20	10%
Breast	65-75%	24	20%
Prostate	65-75%	40	25%
Lung	30-40%	<6	<5%
Kidney	20-25%	6	10%
Thyroid	60%	48	40%
Melanoma	14-45%	<6	<5%

2.2 Pathogenesis of bone metastasis

It's not uncommon for cancer patients to have bone metastasis; that is expected because of the favorable microenvironment of the bone matrix and its abundance of blood supply. Bone metastasis begins when primary tumor cells detach from their place of origin by forming new blood vessels and invade the vasculature. These tumor cells then form aggregates and eventually adhere to the vascular endothelial cells of distant capillaries of the bone. Subsequently, the cells that escape the circulation invades the marrow stroma, and ultimately adhere to the endosteal surface of the bone and proliferate. A variety of factors have been implicated in the metastatic process, including proteolytic enzymes, cell adhesion molecules (CAMs), and growth factors. Proteolytic enzymes are necessary for tumor cells to detach from their primary site, invade the surrounding soft tissue, enter and exit the vasculature, and degrade the bone matrix. Metalloproteinases (MMPs) have been implicated in bone resorption and tumor progression. CAMs, such as integrins, play a critical role in tumor invasion, metastasis, and proliferation Tumor cells secrete parathyroid hormone-related protein (PTHrP) and IL-6, which are powerful mediators of osteoclast activation higher levels of expression are associated with sites of bone metastases (Powell *et al.,* 1991), participate in osteolysis by stimulating the production of receptor activator of nuclear factor-kB ligand (RANKL) by osteoblasts and stromal cells. The RANKL binds to its receptor (Pugh *et al.*) on osteoclast progenitors, leading to the differentiation of the progenitors into mature osteoclasts and initiation of bone resorption.

Simply metastasis of tumor cells to bone requires a complex cascade of actions involving detachment from the primary tumor site, invasion of the vasculature, migration and adherence to distant capillaries of the bone, extravasation,