RETROSPECTIVE ANALYSIS OF 5 YEAR SURVIVAL AND PROGNOSTIC FACTORS OF BREAST CANCER PATIENTS TREATED IN HUSM

BY

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ABSTRAK

Latar Belakang dan Objektif: Kanser payu dara adalah kanser yang paling lazim dan merupakan penyebab utama kematian yang berkaitan dengan kanser and kelazimannya sedang meningkat di Malaysia. Prognosis kanser payu dara adalah lebih baik berbanding kanser-kanser lain, maka tindakan mengenal pasti faktor-faktor prognostik penyakit kanser payu dara memainkan peranan penting dalam proses rawatan pesakit-pesakit ini. Oleh itu, objektif kajian ini adalah untuk menentukan masa hidup 5 tahun untuk pesakit kanser payu dara dan untuk mengkaji peranan faktor-faktor prognostik dalam survival pesakit kanser payu dara di Hospital Universiti Sains Malaysia (HUSM).

Reka bentuk dan kaedah kajian: Ini adalah kajian retrospektif yang dijalankan di Hospital Universiti Sains Malaysia (HUSM). Sejumlah 172 pesakit yang telah disahkan menghidap kanser payu dara dari Januari 2009 sehingga Disember 2013 dimasukkan di dalam kajian ini dan semua pesakit telah diikuti selama 5 tahun daripada tarikh diagnosis dibuat. Sosiodemografi pesakit dan maklumat klinikal dikumpulkan untuk menentukan factor-faktor prognostik. Analisis survival dilakukan dengan menggunakan kaedah Kaplan-Meier, manakala faktor-faktor prognostik survival ditentukan menggunakan analisis regresi Cox.

Keputusan: Survival min bagi pesakit kanser payu dara secara keseluruhan adalah 47.4 bulan dan masa survival min bagi pesakit kanser payu dara untuk kematian berpunca dari kanser payu dara adalah 48.6 bulan. Hasil kajian menunjukkan risiko kematian adalah lebih tinggi untuk saiz ketumbuhan yang lebih besar. Pesakit dengan saiz ketumbuhan T2 mempunyai 9.7 kali ganda lebih tinggi risiko kematian [HR (95% CI): 9.64 (1.97, 47.53), p = 0.005], T3 mempunyai risiko 5.6 kali ganda [HR (95%CI): 5.56 (1.10, 28.04), p = 0.038] dan T4 mempunyai risiko 24.5 kali ganda lebih tinggi [HR (95%CI): 24.49 (5.42, 110.65), p<0.001] untuk kematian berpunca dari kanser payu

dara berbanding dengan saiz ketumbuhan T1. Pesakit yang menunjukkan hasil positif untuk Cerb B2 mempunyai 10kali ganda risiko lebih tinggi untuk kematian berpunca dari kanser payu dara [HR (95%CI): 10.43 (4.49, 24.26), p<0.001]. Rawatan hormone mempunyai fungsi perlindungan terhadap kematian berpunca dari kanser payu dara. Pesakit yang menerima rawatan hormon mempunyai 94% risiko lebih rendah untuk kematian berpunca dari kanser payu dara [HR (95%CI): 0.061 (0.024, 0.151), p<0.001]

Kesimpulan: Kesimpulannya, min masa hidup untuk pesakit kanser payu dara di HUSM adalah 48.6 bulan, dimana ianya lebih rendah berbanding dengan pusat lain. Faktor prognostik penting yang dikenalpasti adalah saiz ketumbuhan, ekspresi Cerb B2, rawatan hormon dan tahap penyakit. Oleh yang demikian, adalah penting untuk mewujudkan kesedaran terhadap kanser payu dara untuk melaksanakan program pencegahan.

ABSTRACT

Background and objective: Breast cancer is the most prevalent malignancy and is one of the leading cause of cancer related mortality and the prevalence is in the increasing trend in Malaysia. The prognosis of breast cancer is better than other malignancies, hence identifying prognostic factors in patients suffering from breast cancer plays a significant role in management. This study aims to determine 5 year survival rate of breast cancer patients and to study the effects of prognostic factors in affecting the survival of breast cancer in HUSM.

Study design and method: This is a retrospective study conducted at Hospital Universiti Sains Malaysia (HUSM). A total of 172 patients with clinically and histologically confirmed diagnosis of breast cancer from January 2009 until December 2013 were included in the study and all patients were followed up for five years from the time of diagnosis. Patients' sociodemographic and clinical information was collected to determine the prognostic factors. Survival analysis was done using the Kaplan-Meier method, while the prognostic factors of survival were determined using the Cox regression analysis.

Result: The mean survival time for overall death were 47.4 months and the mean survival time for breast cancer related death were 48.6 months. The results showed that hazards for breast cancer related death increased as the tumour size increases. . Patients with T2 tumour size has 9.7 times higher hazards [HR (95% CI): 9.64 (1.97, 47.53), p = 0.005], T3 has 5.6 times higher hazards [HR (95%CI): 5.56 (1.10, 28.04), p = 0.038] and T4 has 24.5 times more hazards [HR (95%CI): 24.49 (5.42, 110.65), p<0.001] for breast cancer death compared to T1. Patients with positive Cerb B2

status were found to have 10 times higher hazards for breast cancer compared to negative Cerb B2 status [HR (95%CI): 10.43 (4.49, 24.26), p<0.001]. Hormonal therapy seems to be protective towards breast cancer death as these patients had 94% lower hazards for breast cancer death compared to patients with other treatment methods [HR (95%CI): 0.061 (0.024, 0.151), p<0.001]

Conclusion: In conclusion, the mean survival time for breast cancer patients in HUSM was 48.6 months, which was low as compared to other centres. The significant prognostic factors identified were the tumor size, expression of Cerb B2, hormonal therapy and late stage of disease. Hence it is essential to create better awareness of breast cancer to implement a good prevention and control programme

INTRODUCTION AND LITERATURE REVIEW

Breast cancer is the most common malignancy among women with upto 1.1 million new cases reported yearly worldwide. Breast cancer is also the most prevalent malignant disease overall with estimates looking at one out every nine woman will be diagnosed with breast cancer at a certain point of her lifetime and it is one of the leading cause of cancer related mortality(Lan et al., 2013, Milanović et al., 2013). The prevalence of breast cancer is in the increasing trend in Asian countries and Malaysia shares a similar experience(Abdullah et al., 2013).

The mortality associated with breast cancer varies among different communities and nations and the overall survival rate among developing nations are considerably lower compared to developed countries(Fan et al., 2011, Lan et al., 2013). A half of the number of new cases and 60% of deaths caused by the disease occur in developing countries(Fayer et al., 2016)

The outcome of breast cancer is comparatively better and more favourable than other malignancies such as lung, colon, ovarian and pancreatic cancers. As a consequence to this, identifying prognostic factors in patients suffering from breast cancer plays a significant role in management of these patients(Nordin et al., 2018).

There are various factors that affects survival rate in breast cancer that were identified by a number of literature, such as age at diagnosis, ethnicity, menstrual status, tumour size, stage of the disease, histological grade, hormone receptor status and primary treatment provided(Abdullah et al., 2013, Cappellani et al., 2013, Holzel et al., 2017, Lan et al., 2013, Milanović et al., 2013, Nordin et al., 2018, Rezaianzadeh et al., 2017)

Ethnicity or race has been documented as an important underlying factor that influence the survival rate of breast cancer patients. It has been reported that Malays tend to present at the advanced stage of the disease and likely due to this have a lower survival rate compared to other ethnic groups. Delayed presentation is a known and important factor which influenced the prognosis and survival rate(Bhoo-Pathy et al., 2012, Pathy et al., 2011).

The staging of disease is also recognised as one of the main prognostic factors as those who were diagnosed at a higher stage demonstrated a poorer prognosis for survival time. This result is consistent with previous findings in many studies all over the world(Ali et al., 2011, Bañuelos and María Rosado-Alcocer, 2016, Eng et al., 2016)

Moreover, biological hormonal receptor status has been observed to be a significant factor in the determination of therapy success. Various studies show that patients who were without tumour based hormonal receptors, overall had a worse prognosis and that the presence of hormone receptors is an important factor when determining the therapy required(Mohd Taib et al., 2008, Nematolahi et al., 2018, Eralp et al., 2014)

One of the most important factors influencing the overall survival rate of patients with breast cancer is the presence of distant metastasis as this factor represents the main cause of death in women with breast cancer. Studies showed that the median time to all cause mortality is significantly shorter in those presented with distant spread(Eng et al., 2016)

In Malaysia, there were differences in cultural, health belief and socioeconomic factors among its multi-ethnic communities that may affect their breast cancer survival. A study done in north eastern states of Peninsular Malaysia, particularly found that Malay ethnicity, late stage at diagnosis and no surgical treatment had increased the hazard of death among breast cancer patients in Kelantan.(Nordin et al., 2018).

Although the Chinese has the higher incidence of breast cancer compared to Malays, the prognosis was worst among the Malay ethnic(Abdullah et al., 2013). A study done by Taib et al., (2007) which was conducted in two different settings, namely Kelantan and University Malaya Medical Centre found that 45% patients in rural area used traditional medicine as compared to 15% in urban setting. UMMC had managed more Chinese patients compared to Kota Bharu that managed more Malay patients. This findings might explain that even though a majority number of Kelantanese patients (59%) were diagnosed at early stage, the overall survival rate is poorer among Malays as they prefer to seek traditional options prior to seeking modern treatment.

1.2 RATIONALE OF STUDY

Breast cancer prevalence is in a rising trend worldwide with overall survival rate among Malaysian patients being significantly lower compared to Western population. There are many important prognostic factors that influence the survival of patients with breast cancer as breast cancer is a heterogenous disease which can be determined by various prognostic factors. There are limited number of studies done in Malaysia concerning survival rates of Malaysian women for breast cancers. Henceforth, it is justifiable to provide latest local data of breast cancer patients as it may help and improve the management of breast cancer in HUSM later on. This will indirectly improve the survival of breast cancer patients locally in the region of Kelantan.

2.1 Document submitted for ethical approval

STUDY PROTOCOL

RETROSPECTIVE ANALYSIS OF 5 YEAR SURVIVAL AND PROGNOSTIC FACTORS OF BREAST CANCER PATIENTS TREATED IN HUSM

Protocol number and date: USM/JEPeM/19010071

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Study site :

Hospital Universiti Sains Malaysia (HUSM)

Introduction and Literature Review

Breast cancer is the most prevalent malignant disease and is one of the leading cause of cancer related mortality(Lan et al., 2013, Milanović et al., 2013). The prevalence of breast cancer is in the increasing trend in Asian countries and Malaysia shares a similar experience(Abdullah et al., 2013).

The incidence of death associated with breast cancer differs among different communities and countries and the general survival rate among developing nations are considerably lower compared to developed countries(Fan et al., 2011, Lan et al., 2013). Estimates suggest that half the number of new cases and 60% of deaths caused by the disease may occur in developing countries(Fayer et al., 2016)

The prognosis of breast cancer is comparatively better than other malignancies such as lung, colon, ovarian and pancreatic cancers. As a consequence to this, identifying prognostic factors in patients suffering from breast cancer plays a significant role in management of these patients(Nordin et al., 2018).

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the advanced stage of the disease and likely due to this have a lower survival rate compared to other ethnic groups. Delayed presentation is a known and important factor which influenced the prognosis and survival rate(Bhoo-Pathy et al., 2012, Pathy et al., 2011).

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Other than that, biological hormonal receptor status has been observed to be an important factor in the determination of therapy success. Various studies have determined that patients who were without tumour based hormonal receptors, overall had a worse prognosis and that the presence of hormone receptors is an important factor when determining the therapy required(Mohd Taib et al., 2008, Nematolahi et al., 2018, Eralp et al., 2014)

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Justification of the Study

Breast cancer prevalence is in a rising trend worldwide with overall survival rate among Malaysian patients being significantly lower compared to Western population. There are many important prognostic factors that influence the survival of patients with breast cancer as breast cancer is a heterogenous disease which can be determined by various prognostic factors. There are limited number of studies done in Malaysia concerning survival rates of Malaysian women for breast cancers. Henceforth, it is justifiable to provide latest local data of breast cancer patients as it may help and improve the management of breast cancer in HUSM later on. This will indirectly improve the survival of breast cancer patients locally in the region of Kelantan.

Research question

What is the 5 year survival rate of breast cancer patients in HUSM?

What are the prognostic factors influencing survival of breast cancer patients?

Objective

General:

1. To determine 5 year survival rate of breast cancer patients
2. To study the effects of prognostic factors in affecting the survival of breast cancer in HUSM

Specific:

1) To determine the 5 year survival rate of breast cancer patients in HUSM from 2009 to 2013
2) To determine the prognostic factors influencing survival of breast cancer patients

i) Clinical outcome according to :

- Demographic (Age at diagnosis, Ethnicity)
- Menstrual history (Age of menarche, Menopause status)
- Family history of breast cancer
- Oral contraceptive pills use and Hormone replacement therapy use
- Breastfeeding history
- Tumor size
- Histologic type (Grade, ER/PR status, C-erb B2 expression, Luminal status)
- Stage at diagnosis
- Progression of disease (Local recurrence or New metastases/Progression of metastases)
- Treatment modalities (Surgery, Chemotherapy, Radiotherapy, Hormonal therapy)

ii) Oncological outcome :

- Mean survival time (both overall and disease specific)

Study Hypothesis

Null hypothesis:

There are no associated prognostic factors influencing breast cancer patients survival in HUSM

Alternate hypothesis:

There are associated prognostic factors influencing breast cancer patients survival in HUSM

Methodology

Research design:

This is a retrospective study of patients diagnosed with breast cancer in HUSM from January 2009 to December 2013

Study area:

Kelantan

Reference population:

Breast cancer patients in Kelantan

Source population:

Breast cancer patients diagnosed in HUSM from January 2009 to December 2013, managed under Department of Surgery

Sampling frame:

Patients who are diagnosed with breast cancer in HUSM from January 2009 to December 2013 and meet the inclusion and exclusion criteria

Subject criteria

Inclusion criterias:

1) Patients of all ages, diagnosed with breast cancer as defined by ICD 10 (C50), between periods of 2009 to 2013
2) Traceable records
3) Follow up at least for 5 years
4) Diagnosis based on clinical and histological confirmation

Exclusion criterias:

1) Male patients with breast cancer
2) Diagnosed outside study time frame
3) Breast cancer patients outside Kelantan

Sampling method

No sampling method applied

Sample size estimation

The sample size calculation for this study was done using Power and Sample Size Calculation (PS) Software (version 3, 2009). The significance level (α) was set at 5% and the power study (1- β) was 80%. The hazard ratio (R) (ratio of median survival times of control and experimental group), ratio of control to experimental group (m) and median survival time on control (m1) were obtained from literature. The accrual time (A) for this study will be 60 months. Additional follow up time after end of recruitment (F) will be 60 months. Additional 20% sample size (n) required for considering estimated 20% missing data or loss to follow up.

(α) : Significance level = 0.05

(1- β) : Power = 0.8

(HR) : Hazard ratio = 9.65 (Bhoo Pathy et al., 2011)

(m1) : Median survival time on control treatment = 164 months

(m) : Ratio of control to experimental patients = 4.3

(A) : The accrual time = 60

(F) : Additional follow-up time = 60

(n) : Sample size determination by PS Software (additional 20% for missing data or loss to follow up)

From the calculation the sample size is 172

Research tools

Data collection record sheets

Data collection method

The data will be reviewed and traced from medical records in HUSM record unit. Single researcher will retrieve the required information. Required data will be recorded in data collection sheets

Data analysis

Data will be entered and analysed using SPSS version 24. Survival time will be determined using Kaplan-Meier analysis. To determine the influence of prognostic factors on survival time, Cox Proportional Hazard regression analysis will be used.

Ethical consideration

Subject vulnerability:

Not involving special populations or vulnerable groups

Declaration of absence of conflict of interest:

No conflict of interest in any form

Privacy and confidentiality:

All data collection forms are anonymous and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify individual patients.

Community sensitivities and benefits:

This study will benefit the community by providing a deep insight into our local setting with regards to the overall survival of breast cancer patients and identify differences among multi-ethnic community and their health beliefs which may ultimately be a guide to change our approach to patients from different ethnicities.

Appendix 1

Data collection form

1) **Patient characteristics**
   - i) Date of diagnosis:
   - ii) Name:
   - iii) Age at diagnosis:
   - iv) Age of menarche:
   - v) Address:
   - vi) Registration number:
   - vii) Ethnicity: Malay/Chinese/Indian/Others
   - viii) Menopause status:

Menopaused	
Not menopaused	
Not known	

2) **Personal history**

	Yes	No
Family history		
OCP		
HRT		
Breastfeeding		

3) **Characteristics of breast cancer lesion**

i) Tumour size (cm)

T1 (<2)	
T2 (2-5)	
T3 (>5)	
T4 (skin or chest wall involvement)	

ii) Histological grade

I (well differentiated)	
II (moderately)	
III (poorly)	
Not specified	

iii) Hormone receptor status (+ve/-ve)

ER	
PR	

iv) C-erb B2 status

-ve	
Equivocal	
+ ve	