PRESENTATION, DIAGNOSIS AND TREATMENT OF BREAST CANCER AMONGST WOMEN ATTENDING PUBLIC HOSPITALS IN MALAYSIA: THE TIME INTERVALS AND ASSOCIATED FACTORS TO DELAY

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT

Breast cancer is the commonest form of cancer among women in Malaysia. Although there is a scarcity of data on the relation between delays and survival, it is generally accepted that optimum outcomes are dependent on early detection and adherence to treatment. This study was conducted to evaluate the time intervals and associated factors with delays and non-adherence among breast cancer patients in Malaysia. A multicentre cross-sectional study was conducted in six public hospitals in Malaysia, involving all newly diagnosed breast cancer patients from 1st January to 31st December 2012. Data were collected through medical record reviews and interview by using structured questionnaire. Presentation delay was defined as the time taken from symptoms discovery to first presentation of more than 3 months. Diagnosis delay was defined as the time taken from first presentation to diagnosis disclosure of more than 1 month and treatment delay was defined as the time taken from diagnosis disclosure to initial treatment of more than 1 month. Meanwhile, non-adherence was categorized as any breast cancer patients refusing or discontinuing treatments due to non-medical reasons. Univariable logistic regression and multiple logistic regressions were used for analysis. A total number of 340 patients participated in this study. The median times for presentation, diagnosis, and treatment were 2.4 months, 26 days and 21 days respectively. Presentation delay was seen in 35% of the patients and the factors associated with presentation delay were Kelantan site (OR 4.78; 95% CI: 1.45, 15.7) and complementary and alternative medicine (CAM) use (OR 1.67; 95% CI: 1.01, 2.76). Diagnosis delay was seen in 41.8% and the associated factors were CAM use (OR 2.68; 95% CI: 1.63, 4.41), symptoms without lump (OR 1.98; 95% CI: 1.45, 4.12), having two or more biopsies (OR 3.02; 95% CI: 2.42, 6.45) and having a surgical biopsy (OR 2.56; 95% CI: 1.30, 5.04). Treatment delay was seen in 35.3% and it was associated with localities involving Kuala Lumpur (2) (OR 3.10; 95% CI: 1.48, 6.49), Johor (OR 4.95; 95% CI: 2.13, 11.5), Kelantan (OR 6.68; 95% CI: 2.02,

22.06) and Sarawak sites (OR 3.88; 95% CI: 1.52, 9.88), and those diagnosed at other hospitals (OR 2.18; 95% CI: 1.14, 4.15). Meanwhile, the proportion for non-adherence to surgery was 14%. The factors associated with non-adherence to surgery were localities involving Kuala Lumpur (2) (OR 3.41; 95% CI: 1.00, 11.60), Johor (OR 8.38; 95% CI: 2.38, 29.51) and Kelantan sites (OR 6.32; 95% CI: 1.20, 33.23) and those required mastectomy (OR 5.66; 95% CI: 1.52, 21.03). The proportion for non-adherence to chemotherapy, radiotherapy and hormonal therapy were 30.1%, 33.3% and 36.3% respectively and the only independent factor associated with non-adherence to oncology therapy was the Perak site (OR 1.42; 95% CI: 1.18, 1.97). Delays in presentation, diagnosis, and non-adherence to treatment were high among breast cancer patients attending public hospitals in Malaysia. Factors influencing delays and non-adherence were multifactorial implicating a complex interaction between variations influence of socio-culture, patients and health systems in Malaysia. Mutual collaboration from multiple areas involving patients and multidisciplinary healthcare sectors are important to reduce delays and non-adherence to treatments. Therefore, a comprehensive intervention study and audits are suggested to improve breast cancer care quality in Malaysia.

ABSTRAK

Kanser payudara sering berlaku di kalangan wanita di Malaysia. Walaupun kekurangan data mengenai hubungan kelewatan dan survival, ianya diterima secara umum bahawa hasil optimum rawatan adalah bergantung kepada pengesanan awal dan pematuhan rawatan. Kajian ini dijalankan untuk menilai selang waktu dan faktor-faktor yang berkaitan dengan kelewatan dan ketidakpatuhan dalam kalangan pesakit kanser payudara di Malaysia. Satu kajian keratin rentas pelbagai-pusat telah dijalankan di enam hospital awam di Malaysia. Semua pesakit kanser payudara yang baru didiagnosis dari 1 Januari hingga 31 Disember 2012 telah diambil. Data dikumpulkan melalui rekod perubatan kajian dan temu bual dengan menggunakan soal selidik berstruktur. Kelewatan kehadiran ditakrifkan sebagai masa yang diambil dari gejala penemuan sehingga persembahan pertama lebih daripada 3 bulan. Kelewatan diagnosis ditakrifkan sebagai masa yang diambil daripada persembahan pertama sehingga pendedahan diagnosis lebih daripada 1 bulan dan kelewatan rawatan ditakrifkan sebagai masa yang diambil daripada pendedahan diagnosis sehingga rawatan awal lebih daripada 1 bulan. Sementara itu, ketidakpatuhan dikategorikan sebagai mana-mana pesakit kanser payudara yang enggan atau memberhentikan rawatan atas sebab-sebab bukan perubatan. Regresi logistik univariat dan regresi logistik multivariat digunakan untuk analisis. Seramai 340 pesakit telah mengambil bahagian dalam kajian ini. Masa median untuk kehadiran, diagnosis dan rawatan adalah masing-masing selama 2.4 bulan, 26 hari dan 21 hari. Kelewatan kehadiran adalah 35% dan faktor-faktor yang berkaitan adalah lokasi di Kelantan (OR 4.78; 95% CI: 1.45, 15.7) dan penggunaan rawatan sampingan dan alternatif (OR 1.67; 95% CI: 1.01, 2.76). Kelewatan diagnosis adalah 41.8% dan faktor-faktor yang berkaitan adalah penggunaan rawatan sampingan dan alternatif (OR 2.68; 95% CI: 1.63, 4.41), simptom tanpa benjolan (OR 1.98; 95% CI: 1.45, 4.12), menjalani dua atau lebih biopsi (OR 3.02; 95% CI: 2.42, 6.45) dan menjalani biopsi pembedahan (OR 2.56; 95% CI: 1.30,

5.04). Kelewatan rawatan adalah 35.3% dan faktor-faktor yang berkaitan adalah lokasi di Kuala Lumpur (2) (OR 3.10; 95% CI: 1.48, 6.49), Johor (OR 4.95; 95% CI: 2.13, 11.5), Kelantan (OR 6.68; 95% CI: 2.02, 22.06) dan Sarawak (OR 3.88; 95% CI: 1.52, 9.88), dan pesakit yang didiagnosis di hospital lain (OR 2.18; 95% CI: 1.14, 4.15). Sementara itu, peratusan bagi ketidakpatuhan kepada pembedahan adalah 14%. Faktor-faktor yang berkaitan dengan ketidakpatuhan kepada pembedahan adalah lokasi di Kuala Lumpur (2) (OR 3.41; 95% CI: 1.00, 11.60), Johor (OR 8.38; 95% CI : 2.38, 29.51) dan Kelantan (OR 6.32; 95% CI: 1.20, 33,23) dan mereka yang memerlukan mastektomi (OR 5.66; 95% CI: 1.52, 21.03). Peratusan bagi ketidakpatuhan kepada kemoterapi, radioterapi dan terapi hormon adalah masing-masing 30.1%, 33.3% dan 36.3%. Hanya satu faktor yang berkaitan dengan ketidakpatuhan kepada terapi onkologi iaitu lokasi di Perak (OR 1.42; 95% CI: 1.18, 1.97). Kelewatan kehadiran, diagnosis, dan ketidakpatuhan kepada rawatan adalah tinggi di kalangan pesakit kanser payudara yang menghadiri hospital-hospital awam di Malaysia. Faktor-faktor yang mempengaruhi kelewatan dan ketidakpatuhan adalah multifaktor melibatkan interaksi kompleks antara variasi pengaruh sosio-budaya, pesakit dan sistem kesihatan di Malaysia. Kerjasama dari pelbagai bidang yang melibatkan pesakit dan pelbagai disiplin sektor penjagaan kesihatan adalah penting untuk mengurangkan kelewatan dan ketidakpatuhan kepada rawatan. Oleh itu, kajian intervensi menyeluruh dan audit disarankan untuk meningkatkan kualiti penjagaan kanser payudara di Malaysia.

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LIST OF SYMBOLS AND ABBREVIATIONS

A&E	:	Accident & Emergency
AJCC	:	American Joint Committee on Cancer
BC	:	Breast clinic
BCS	:	Breast conserving surgery
BSE	:	Breast self-examination
CAM	:	Complementary and alternative medicine
CB	:	Core biopsy
CBE	:	Clinical breast examination
CI	:	Confidence Interval
CPG	:	Clinical practice guideline
FNAC	:	Fine needle aspiration
GP	:	General practitioner
HKL	:	Hospital Kuala Lumpur
HRPB	:	Hospital Raja Permaisuri Bainun
HRPZII	:	Hospital Raja Perempuan Zainab II
HSI	:	Hospital Sultan Ismail
HUS	:	Hospital Umum Sarawak
KK	:	*Klinik kesihatan*
MAC	:	Mastectomy
MMG	:	Mammogram
OPD	:	Out-patient department
OR	:	Odd ratio
SD	:	Standard deviation

SOPD	:	Surgery out-patient department
UMMC	:	University Malaya Medical Centre
US	:	Ultrasound

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Outline of this chapter

The chapter introduces to the background of this study, the problem statement, the justification and the objectives of this study. All of the components mentioned therein are intended for the purpose for this study being conducted.

1.2 Background of the study

Breast cancer is one of the most prevalent cancer which has caused the highest mortality rate among women worldwide. It is estimated that 1.7 million women were diagnosed with breast cancer and 522, 000 of deaths were reported due to breast cancer (GLOBOCAN, 2012). Since 2008, there is a sharp increase of women diagnosed with breast cancer with incidence of the said cancer have been reported to escalate by 20% and mortality rate by 14% (Ferlay et al., 2013). The rampant and extensive rise of cases involving breast cancer is strong indication that active prevention and efficient control should be given the utmost priority by all global health authorities.

The said increase of cases involving breast cancer however shows there is a discrepancy in statistics between developed and developing countries, as evidenced by declining death rates in the developed nation. For instance, the 5-year overall survival rate in the US was 89% (American Cancer Society, 2015) as compared to 49% in Malaysia (Abdullah et al., 2013).

Better survival in developed countries is generally attributed to a combination of the success of operational screening programs, earlier detection and efficient treatment (Schwentner et al., 2013), but these advances are very much limited in developing countries. Hence, this calls for an urgent need to develop effective yet affordable

approaches of prevention in cancer control, especially breast cancer with significant approaches in the shortening delays of presentation, diagnosis and treatment among breast cancer patients in developing countries.

It is evident that delays in presentation, diagnosis and treatment of breast cancer have been shown to cause an impact in arriving at the disease prognosis (Richards et al.,1999), thus this study highlights the need to evaluate issues of delays and non-adherence of breast cancer treatments in Malaysia. On the other hand, the optimal time for the presentation, diagnosis and treatment of breast cancer cannot be defined and recommended to patients without evidence on the impact on the outcome. Moreover, there is a want of information in Malaysia among patients attending public hospitals on what constitutes as an acceptable duration of time intervals in breast cancer and this study is concerned with whether this should be used as a quality indicator. Therefore, it is important to analyze into the local population particularly on the time used to presentation, diagnosis and treatment of breast cancer to determine the factors related to delays and non-adherence in Malaysia.

This study also proposes that one of the issue that should be highlighted is that there are considerable uses of complementary and alternative medicine (CAM) amongst breast cancer patients (Al-naggar et al., 2013; Muhamad et al., 2012). Although there is no evidence that claim CAM is more effective than conventional medicine, the public shows growing preference and reliance in CAM. However, the significant and implication caused by the usage of CAM to the efficacy of conventional medicine remains unclear. Therefore, it is also important to evaluate whether the use of CAM among breast cancer patients can be associated with delays in presentation, diagnosis or treatment of breast cancer in Malaysia.

Through this study, it is hoped that the impact of delays on survival, time intervals of breast cancer, associated factors to delays and non-adherence, and relationship between complementary and alternative medicine (CAM) use and delays could be identified. Therefore, a more systematic and effective intervention could be applied towards women to shorten delays, thus improve the patients' survival and cancer care performance in Malaysia.

1.3 Delays in breast cancer

The terminology of 'Breast Cancer Delay' was first introduced by Pack & Gallo, (1938) which was intended to look at the perspective of time delays in the whole system, which begins from symptom discovery and the initiation of medical treatment. It is considered from both factors; the patients and the health system. The type of delay is then divided into three time intervals which are presentation, diagnosis and treatment (Unger-Saldaña & Infante-Castañeda, 2011).

Presentation delay is calculated from symptom discovery to first presentation (Cheng et al., 2015; Ghazali et al., 2013; Harirchi et al., 2005). Whereas, diagnosis delay is calculated from first presentation to a diagnosis disclosure (Ermiah et al., 2012; Huo et al., 2014; Plotogea et al., 2014). Finally, treatment delay is calculated from a diagnosis disclosure to initiation of medical treatment (Pérez et al., 2008; Rastad et al., 2012; Shandiz et al., 2012).

1.4 Problem statement

Delays in getting medical attention are common in breast cancer. This issue is important as delays adversely affects prognosis, which will then lead to the progression to a more advanced stage of breast cancer (Richards et al., 1999) and bigger tumor size (Montazeri et al., 2003; Samphao et al., 2009), thereby leading to a reduced survival (Yun et al., 2012; Jung et al., 2011; Richards et al., 1999). However, there are conflicting

findings of the delays associated with longer survival (Brazda et al., 2010; Sainsbury et al., 1999; Samur et al., 2002). It is not known at present, how systematically a delay in time affects breast cancer survival. The impact of delays on survival is still unclear in Malaysia and requires a more detailed study.

Studies on delay in presentation, diagnosis and treatment of breast cancer among patients in public facilities are scarce in Malaysia. There are only few studies giving particular attention on the time interval of the breast cancer journey. Furthermore, there is no national baseline data available that would indicate periods of complete intervals from discoveries of symptoms until the onset of treatment. Therefore, it is timely appropriate to study into the time intervals of breast cancer journey, especially on the time taken to presentation, diagnosis and treatment among breast cancer patients attending public hospitals in Malaysia.

It should be noted however, that there was only one study conducted on the time intervals of breast cancer in Malaysia (Lim et al., 2014). However, the issue with that particular study is that most of the locations where the study was conducted were mainly involving private and a university hospital in the urban settings where cancer specialists, manpower and physical infrastructure are concentrated. Furthermore, only patients with complete data were included in that particular study. Therefore, the results are likely to be perceived better than they really were and not likely to be represent the general population in Malaysia.

It is also observed that there is no consensus of an acceptable duration for presentation, diagnosis and treatment of breast cancer due to limited data in Malaysia. The ‘Clinical Practice Guideline for Management of Breast Cancer’ in Malaysia has proposed one time interval of two months interval from presentation to treatment as clinical audit indicators of the system quality management (Ministry of Health Malaysia,

2010). Nonetheless, the distributions of the other time intervals are not routinely available. The time to presentation after symptom discovery, followed by time to referral, biopsy, pathology reports, diagnosis disclosure and time to treatment; surgery, chemotherapy, radiotherapy and hormonal therapy are yet to be proposed. Therefore, this study asserts that the time intervals in breast cancer should be precisely defined for a better evaluation.

In Malaysia, there is no available recorded statistics or benchmark to enumerate the quality of breast cancer care services. A comparison made between Asian countries and the rest of the world regarding the performance of breast cancer care is difficult to be computed. Although there are guidelines for timeframes provided by western countries that can be used as reference, the time element for each delay interval being used in scientific papers and policy documents varies, causing difficulties in selecting the most proper timeframe and may not be suitable for adaptation to our local population.

Given that breast cancer patients in Malaysia may continue to delay presentation, diagnosis and treatment, it is a priority for Malaysian researchers to identify the associated factors pertaining to breast cancer delays. Clearly large number of breast cancer patients in Malaysia received care in less well-resourced settings (Lim et al., 2014). However, little is known about the breast cancer care amongst patients attending public hospitals in Malaysia. Therefore, a multicentre study nationwide composed of patients from diverse socio-demographic background from various locations of public hospitals would provide a better picture of breast cancer delays, thus making it possible to infer to the Malaysia population.

The duration of breast cancer treatment is relatively long, especially during the period of chemotherapy, radiotherapy and hormonal therapy. Patients are required to attend hospital regularly for chemotherapy and radiotherapy, and need to undergo

hormonal therapy which can last up to 5 years to obtain the maximum benefits. However, longer treatment duration especially during the lengthy hormonal therapy has been highlighted as a potential problem to non-adherence (Aalto, 2013). Refusal to or defaulting treatments may result in disease progression as well as increased costs and consumption of health care resources. Therefore, a study to evaluate non-adherence to treatment among breast cancer patient in Malaysia is urgently needed.

Complementary and alternative medicine (CAM) has become increasingly popular among breast cancer patients in Malaysia (Al-naggar et al., 2013; Muhamad et al., 2012). CAM use has been cited as a cause of delays in breast cancer in qualitative studies (Norsa'adah et al., 2012; Taib et al., 2011) but there had not been any confirmatory study that can validate its impact on delays. Moreover, studies on CAM use amongst breast cancer patients in Malaysia are more focused on the prevalence and its associated factors (Al-naggar et al., 2013; Knight et al., 2015; Saibul et al., 2012); type and pattern (Farooqui et al., 2015; Raja et al., 2013); purposes (Muhamad et al., 2012); knowledge (Yew et al., 2015); and quality of life (Chui et al., 2015). There are limited published reports on CAM use and its impact on conventional cancer treatments. Therefore, the relationship between CAM use and delays in breast cancer should be studied extensively to investigate the association of CAM use and delays in breast cancer.

1.5 Justification of study

The impact of delay in breast cancer towards reducing survival is still unclear (Richards et al., 1999; Sainsbury et al., 1999). Cancer stage, lymph node status, tumor size and tumor grade were known as prognostic factors in breast cancer survival (Taib et al., 2008). Meanwhile, delays in presentation, diagnosis and treatment of breast cancer are a good indicator for a better quality of breast cancer care. Although there is a lack of

data on the relationship between delays and survival rates, early detection and prompt treatment are generally accepted for optimum outcomes (Sy, As, & Yte, 2015).

Due to the heterogeneous nature of breast cancer, individual patient would behave differently based on their grade of tumor. A slow-growing tumor would be less harmful compared to a fast-growing tumor as seen in a study which reported that survival is not related to the delay alone but to the grade of the tumor (Bloom, 1965). Although the available treatment for breast cancer is known to have good prognosis in early detection, delays remain as the main obstacle in obtaining better prognosis. Unfortunately, there is no predictive model to identify which patients who would be afflicted with aggressive type of cancer. Therefore, a strategy to reduce delay in presentation, diagnosis and treatment may prove to be useful. The time intervals are generally accepted to be kept at minimum as early intervention result in better quality of life (Sy et al., 2015). The earlier the patient present, diagnosed and treated, the better the breast cancer prognosis.

Since delays are related to poor prognosis, one would believe that it is important to minimize delays in presentation, diagnosis, and treatment of breast cancer. Longer waiting times prior to breast cancer detection, diagnostic and the initiation of therapy are the prognostic concern if delay leads to stage progression, disease worsening, or treatment complications. In many countries, timely access to health care services has become a priority in public health policies (Burgess et al., 1998; Caplan et al., 2000; Landercasper et al., 2010). The time interval is an indicator not only for the accessibility to health care providers but also to show inequalities of care in patient management. Efforts to reduce delay or waiting time have been emphasized in practice guidelines (Ermiah et al., 2012). Although the Clinical Practice Guidelines (CPG) for breast cancer in Malaysia has recommended two months interval from presentation to initial treatment (Ministry of

Health Malaysia, 2010), there are no studies or audits that have been done to assess these guidelines.

The delays in presentation, diagnosis and treatment are attributed mainly to the various barriers that exist in Malaysia. Malaysia has no population-based screening program (Dahlui et al., 2013) for early detection of breast cancer and access to early medical attention (Yip et al., 2008). This has made worse by the lack of information and the negative perception of breast cancer among the community (Norsa'adah et al., 2012; Taib et al., 2014) and widely use of complementary and alternative medicine (CAM) among the breast cancer patients (Chui et al., 2015; Farooqui et al., 2015; Saibul et al., 2012; Taib et al., 2013).

Therefore, early actions with comprehensive planning should be taken into active considerations to solve these issues at stake. Improving breast health literacy in developing countries especially Malaysia remains a challenge that may be overcome with collaboration from multiple areas; involving patients and multidisciplinary of health care sectors.

1.6 Research question

1. What are the time intervals and factors associated with delays in presentation, diagnosis and treatment of breast cancer from both perspective of patient and the health system in Malaysia?

1.7 General objective

This study aims to determine the time intervals and factors associated with delay in presentation, diagnosis and treatment of breast cancer patients at public hospitals in Malaysia.

1.8 Specific objective

The main objectives for this study to be carried out are as follows;

1. To evaluate the impact of time to primary treatment after a diagnosis of breast cancer and overall survival.
2. To determine the time intervals between important time points in the breast cancer journey from symptom discovery to initial treatment.
3. To determine the proportion of delays in presentation, diagnosis and treatment of breast cancer patients.
4. To determine the factors associated with delays in presentation, diagnosis and treatment of breast cancer patients.
5. To determine factors associated with non-adherence to breast cancer treatments (e.g. surgery, oncology therapy) amongst breast cancer patients.
6. To determine the associated factors of CAM use amongst breast cancer patients and its relationship with delays in presentation, diagnosis and treatments of breast cancer.

1.9 Focus and organization of thesis

The thesis is divided into six chapters which are briefly introduced below;

Chapter 1 – Introduction: All components described in this chapter spells out the main purpose on why the study needs to be conducted.

Chapter 2 – Review of the literature: This chapter describes the present situation of the problem in terms of epidemiology and statistics, as well as a series of previously published study and current knowledge. The conceptual framework which guided the research is elaborated upon to explain the study problems.

Chapter 3 – *Delay in time to primary treatment after a diagnosis of breast cancer and impact on overall survival:* This chapter addresses a specific research objective and related topic of the study and consists of its own sections for the introduction, brief literature review, methodology, results, discussion, limitations, contribution, implication, and conclusion.

Chapter 4 – *Presentation, diagnosis and adherence to treatment of breast cancer patients attending public hospitals in Malaysia: The time intervals and associated factors to delay and non-adherence.* This chapter addresses some of the specific research objectives and related topic of the study and consists of its own sections for the introduction, brief literature review, methodology, results, discussion, limitations, contribution, implication, and conclusion.

Chapter 5 – *Complementary and alternative medicine (CAM) use and delays in presentation, diagnosis and treatment of breast cancer patients in public hospitals in Malaysia.* This chapter addresses a specific research objective and related topic of the study and consists of its own sections for the introduction, brief literature review, methodology, results, discussion, limitations, contribution, implication and conclusion.

Chapter 6 – Conclusion: This final chapter summarizes the research findings in all articles and recommendations stemming from the research as well as the contributions, implication for policy, practice and suggestions for future research.

1.10 Chapter summary

Delays in getting medical attention are common in breast cancer. This issue is important as delay adversely affects prognosis. This study was carried out to document the experience of Malaysian women presenting with breast cancer with regards to their presentation, diagnosis and treatment, as well as to understanding the associated factors

of delays and non-adherence towards treatment and impact on complementary and alternative medicine (CAM) use on delays in breast cancer.

This study is the first to report a multi-social and multi-cultural evaluation on complete breast cancer journey which begins from the symptom discovery until completion of treatment amongst patients attending public hospitals in Malaysia. With this baseline study on the time taken to presentation, diagnosis and treatment of breast cancer and its associated factors to delay and non-adherence, intervention and health promotion strategies can be carried out more effectively in the future.

CHAPTER 2: LITERATURE REVIEW

2.1 Outline of this chapter

In this chapter, a literature review is carried out to familiarize the readers with practical issues relating to the research problems. This chapter highlights on the literature search and the loopholes in the literature that need further exploration while laying the foundation for the study.

This chapter describes the procedures on how the literature review was conducted, followed by the country profile, history of breast cancer, epidemiology, biology, management and the present situation on breast cancer. Similar concepts have emerged from numerous primary studies and reviews done internationally and also in the Malaysian settings. To simplify the findings, summaries of articles have been extracted and presented based on the three categories of presentation delay, diagnosis delay, treatment delay.

Structured views about delays in breast cancer from both perspectives of patient delay and system delay are given in this chapter. The generic health behaviour theories and the bio-psychosocial model of health care and exploratory delay theories are presented. Reviews on the time intervals, cut-off points and factors contributing to the delays in breast cancer, add perceptive to the research topic. Topics concerning adherence to cancer treatments and the impact of delays on patient and survival are highlighted for deeper understanding.

In the last section of this chapter, a conceptual framework of the time intervals and the various factors contributing to delays in breast cancer concerning on presentation, diagnosis and treatment are described based on the literature review.

2.2 Literature review procedures

2.2.1 Literature search

Potential publications describing the breast cancer delay and its associated factors were identified, mainly by searching electronic databases. Studies within the period of January 1990 to June 2015 from the ScienceDirect, Proquest, PubMed, and MEDLINE were accessed. Keywords or search terms that focused on breast cancer delay were used to search for articles and research findings. All related keywords, text words and search terms were identified and used for the literature search. Search terms related to delays in breast cancer used in this review includes: presentation delay, diagnosis delay and treatment delay. Subsequently, the breast cancer delay was searched individually in other types of delay: total delay, patient delay, late presentation, delay in seeking help, delay of medical care, system delay, provider delay and late-stage diagnosis. In addition, search terms related to impact of delay and compliance or adherence of breast cancer treatments were also used. Lastly, researching the local journals, follow up reference lists of key papers and relevant reviews were conducted to locate additional publications that were not accessible through electronic databases.

2.2.2 Study Selection

Inclusion criteria for this review are; 1) primary research of cross-sectional, prospective and retrospective cohort study designs, 2) studies conducted on histopathology diagnosed breast cancer patients 3) studies assessing delays, time taken between important time points in breast cancer journey and non-adherence to breast cancer treatments, and 4) studies conducted from January 1990 to Dec 2015. In contrast, exclusion criteria included studies which are; 1) not involving the breast cancer patients and 2) did not based on histopathology diagnosis.

2.2.3 Data Extraction & Outcome Measures

Following the initial search, reference list was imported to reference manager software, Mendeley Desktop version 1.15.2. Researchers independently assessed potentially relevant articles for eligibility after eliminating duplications. Selection of articles underwent three stages; selection based on titles, followed by abstract consideration and finally by assessing the full text. Any differences of opinions were resolved through discussion prior to consensus made.

The outcomes of interest are breast cancer delay; presentation delay, diagnosis delay and treatment delay**.** Data was extracted for each finalized study and were included for systematic review. The data extraction form was used to gather information on population and its' setting (i.e. population description, location, inclusion and exclusion criteria, method of recruitment and consent), methodology of the study (i.e. objective, design, study duration and ethical approval), risk of bias assessment, participants (i.e. number of the study participants, withdrawals, exclusions, characteristics of the study participants), calculations (i.e. time interval/duration between important time points in breast cancer journey) and outcomes (i.e. survival, delay, non-adherence, complementary and alternative medicine use).

The assessments of methodological quality of the included studies were undertaken independently and disagreements were discussed. The study was assigned to either three groups of category: high quality data, acceptable or unacceptable information based on the methodological quality to minimize bias.

2.3 Malaysia

2.3.1 Country Profile

Country profile is carried out to familiarize the readers with geographical information relating to the study. Malaysia is located at South-East Asia and has a total landmass of 329,847 square kilometres. It consists of thirteen states separated by the South China Sea into two similarly sized regions, Peninsular Malaysia and East Malaysia. In 2010, the population was 28.33 million, with 22.6 million living in the Peninsular. The Malaysian Census 2010 revealed that an average annual population growth rate of 2.0% for 10 years period, 2000-2010 (Department of Statistic Malaysia, 2012). Malaysian citizens contributed 91.8% of the total population while 8.2% were non-citizens. Malaysian citizens consist of the ethnic groups of Bumiputera (67.4%), Chinese (24.6%), Indians (7.3%) and others (0.7%). Malays (63.1%) are the predominant ethnic group and Islam (61.3%) is the most widely professed religion in Malaysia. Other religions are including Buddhism, Christianity, and Hinduism (Department of Statistic Malaysia, 2012).

Figure 2.1: South-East Asia Regions

(Source: http://journeymart.com/de/south-east-asia.aspx. Accessed online on 21 September 2016)

2.3.2 Demography and Social Development

In 2010, 19.8 million people out of 28.3 million in Malaysia were under 40 years of age. There were 5.4 million adolescents (10-19 years) which represent 19% of the total population. The proportion of the population age 15 to 24 years was 18.4% (5.2 million) while the proportion of 25 to 39 year age group was 24.1% (6.8 million) of the total population (Department of Statistic Malaysia, 2012).

The Malaysian Census 2010 showed that population age of 15 years and above who never married were 34.5% while those who were married were 60.0%. Women have atendency to marry at a later age, with mean age of first marriage at 25.8 years in 2010 compared to 25.1 years in 2000 (Department of Statistic Malaysia, 2013).

In 2012, most people lived in urban areas (72.8%) with a literacy rate of 97.3% and school attendance of 95.8% in 2010 (Department of Statistic Malaysia, 2013a). Total fertility rate was 2.1 in 2012. Maternal mortality was 29 deaths per 100,000 live births and contraceptive rate was 54.5% (Department of Statistic Malaysia, 2013).

2.3.3 Life expectancy

According to the latest WHO data published in 2015, total life expectancy in Malaysia was 75.0 with 72.7 for male and 77.3 for female which gives Malaysia a World Life Expectancy of 66th in the world. Meanwhile, the Breast Cancer Deaths in Malaysia reached 2,535 or 1.99% of total deaths according to the latest WHO data published in May, 2014. The age adjusted death rate was 19.88 per 100,000 of population ranks Malaysia to 54th in the world (WHO, 2015).

2.3.4 Health Services

The provision of health care services is divided into three levels; federal, state and district levels. Health services are provided through a nationwide network of 143 public hospitals (14 state hospitals, 24 major specialist hospitals, 19 minor specialist hospitals, 76 non-specialist hospitals and 10 special medical institution) (Ministry of Health Malaysia, 2015) and 2,860 public health clinics (1,039 health clinic, 1,821 community clinics) (Ministry of Health Malaysia, 2015).

The service provision is facilitated through the hierarchical system, begins from primary care, secondary care and tertiary care. The Malaysia Ministry of Health (MOH) is the main government agency responsible for formulating the health policies and delivering public health care in Malaysia. Strong economic growth rates allowed continuity in investment in public health and substantial improvements in the oncological health services which by 2010, more than 85% of people had access to free health services within five kilometres from their residence (Rashidah, 2009).

There are no problems in accessing affordable health services for Malaysian citizens as the government provides almost free and highly subsidised healthcare. However, there are several limitations of breast cancer care in Malaysia, whereby the mammography screening remains under-utilized and it is solely depending on the women decision to self-refer themselves for screening (Yip et al., 2014). Besides, little is known on the efficiency in cancer care as there is no national audit for breast cancers in Malaysia. Therefore, further study on cancer services should be done as it could assist clinicians and policy makers to improve strategies and implement better public health activities of breast cancer in the future.

2.4 Breast cancer epidemiology

2.4.1 Worldwide

Breast cancer is the second most common cancer in the world after lung cancer. It is the most frequent cancer found among women with an estimated 1.67 million new cancer cases diagnosed in 2012, which comprised 25% of all cancers diagnosed in that year. It is the most common form of cancer in both more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000 cases) regions. The incidence of cancer varies with 92 per 100,000 population in Northern America to 27 per 100,000 population in Middle Africa and Eastern Asia (GLOBOCAN, 2012).

Breast cancer is the fifth cause of death from cancer overall (522,000 deaths). It is the most frequent cause of cancer related death in women in less developed regions (324,000 death, 14.3% of total) and currently the second cause of death in more developed regions (198,000 deaths, 15.4%). The range in mortality rates between world regions is less than incidence rates because there are more survival of breast cancer in high-incidence of developed regions, with rates ranging from 6 per 100,000 population in Eastern Asia to 20 per 100,000 population in Western Africa (GLOBOCAN, 2012). Figures below show the estimated incidence of breast cancer worldwide in 2012.

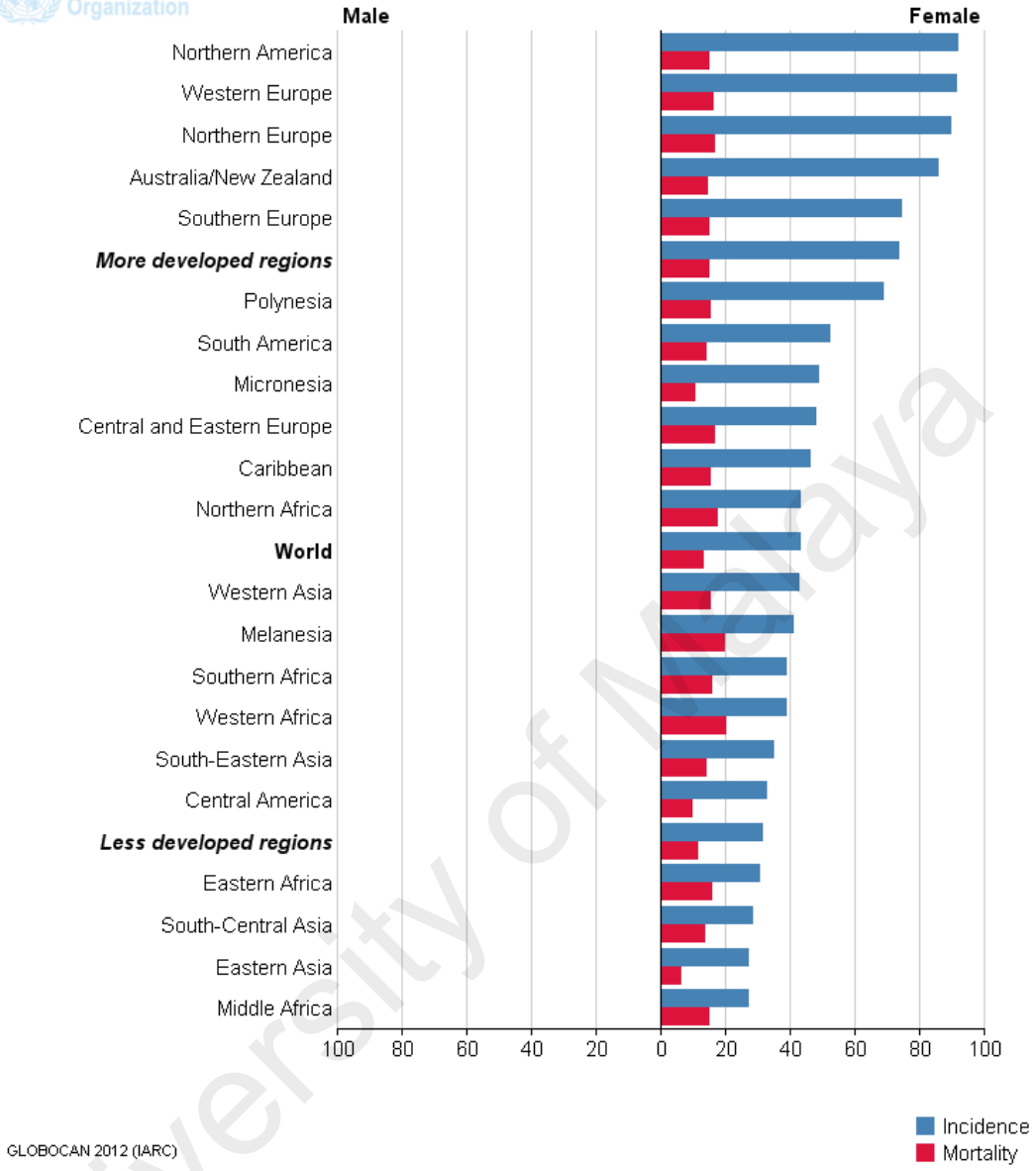


Figure 2.2: Incidence and mortality rates of breast cancer in 2012

(Source: Globocan Report 2012, www.globocan.iarc.fc. Accessed online on 8 September 2016)

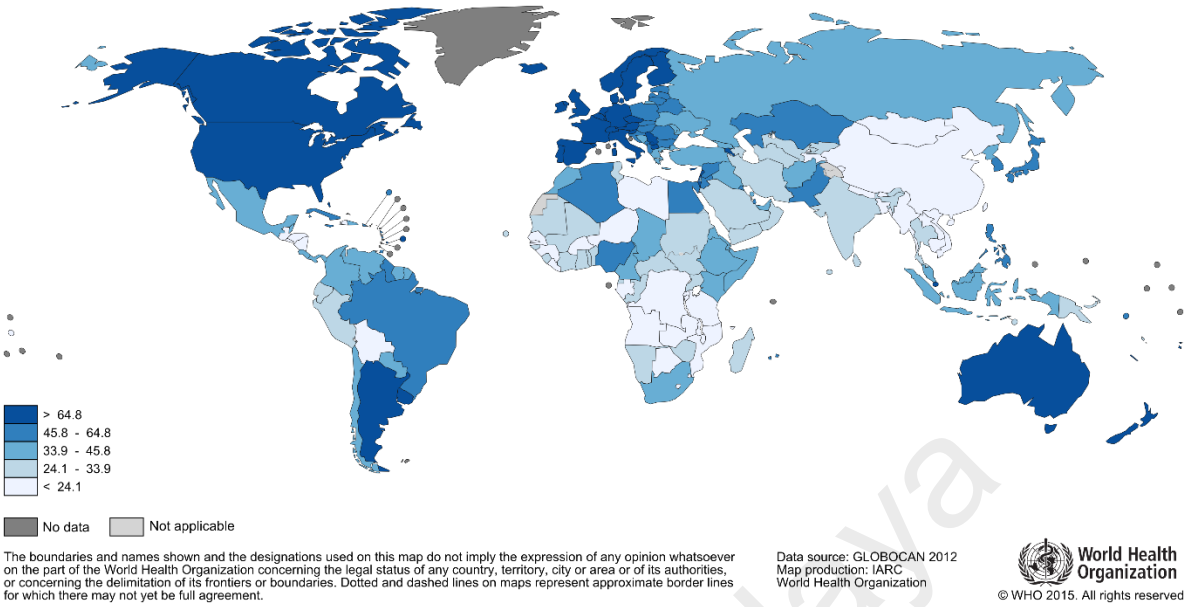


Figure 2.3: Incidence of breast cancer in 2012 - Estimated age-standardised rates per 100,000 population

(Source: Globocan Report 2012, www.globocan.iarc.fc. Accessed online on 8 September 2016)

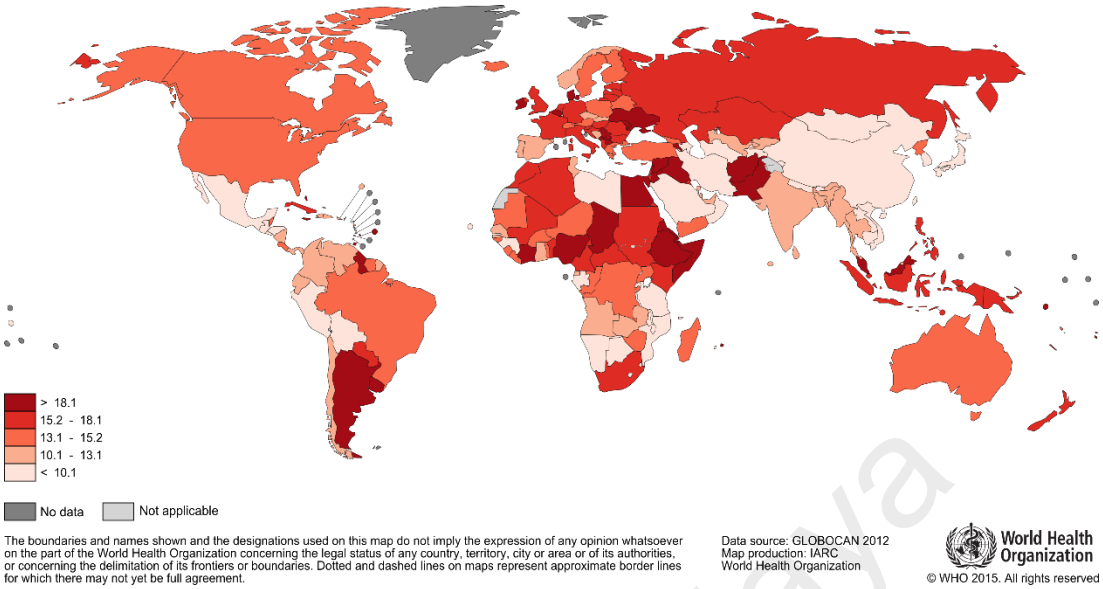


Figure 2.4: Mortality of breast cancer in 2012 - Estimated age-standardised mortality rates per 100,000 population

(Source: Globocan Report 2012, www.globocan.iarc.fc. Accessed online on 8 September 2016)

2.4.2 Breast cancer in South-East Asia

There is an increase of breast cancer incidence in the South-East Asia regions whereby approximately, 240,000 of new cases were diagnosed in 2012 with an overall age-standardized rate (ASR) of 34.8 per 100,000 populations in South-East Asia. The incidence of breast cancer varies with 19.0 per 100,000 population in Laos to 65.7 per 100,000 population in Singapore. The ASR of breast cancer for other regions are 48.6 in Brunei, 47.0 in Philippines, 40.3 in Indonesia, 38.7 in Malaysia, 32.6 in Timor-Leste, 29.3 in Thailand, 23.0 in Vietnam, 22.1 in Myanmar, and 19.3 in Cambodia per 100,000 population (GLOBOCAN, 2012).

Breast cancer is a common cause of death by cancer among women in South-East Asia regions (110,000 deaths). The mortality rates in the South-East Asia regions ranges from 9.3 per 100,000 population in Laos to 18.9 per 100,000 population in Malaysia (GLOBOCAN, 2012). Singapore reported the highest incidence rate but lower mortality rate than Malaysia, indicating better survival is achieved in that country.

2.4.3 Breast cancer in Malaysia

Breast cancer is the most common cancer among women in Malaysia (Yip et al., 2014). Approximately 3,242 of new breast cancer cases was reported in 2007 (Zainal Ariffin & Nor Saleha, 2011) and an estimate of 5,410 cases was reported in 2012 (GLOBOCAN, 2012). The age-standardized rate (ASR) was peak at the 50-59 age groups, with 29.1 per 100,000 populations in 2007 (Zainal Ariffin & Nor Saleha, 2011) and increased to 38.7 per 100,000 in 2012 (GLOBOCAN, 2012). The breast cancer incidence is highest among Chinese (38.1 per 100,000) followed by Indian (33.7 per 100,000) and Malay (25.4 per 100,000) (Zainal Ariffin & Nor Saleha, 2011).

Over the 12-year period from 1993 to 2004, about 60-70% of women presented with early stage (Stages 1- 2) while 30-40% presented with late breast cancer (Stages 3-4). An

updated have been done by the National Cancer Registry in 2010 and similar figures were found with 21%, 37%, 24% and 18% were diagnosed at stage I, II, III and IV respectively. Selangor site (40.8%) was reported as the highest incidence of breast cancer (Zainal Ariffin & Nor Saleha, 2011).

Breast cancer survival in Malaysia is lower compared to the developed countries. The 5-year overall survival rate in Malaysia was only 49% (Abdullah et al., 2013) as compared to 70% in Singapore (Chang, Chan, & Hartman, 2011) and >80% in England and US (American Cancer Society, 2015; Redaniel et al., 2015). Between the ethnicities, Malays had the lowest survival rate (45-58%), present at later stages and with larger tumors as compared to Chinese and Indian patients (Cheng Har Yip et al., 2006; Bhoo-Pathy et al., 2012; Abdullah et al., 2013).

The commonest presenting symptom was a lump in the breast in over 90% of cases, generally felt by the woman herself. The mean size of the lump was 4.2 cm, and on average, the women waited 3 months before seeking medical attention (Cheng Har Yip et al., 2006). Results from studies conducted on breast cancer in Malaysia found that patients presented to primary care between 2 to 4 months after discovering symptoms (Alfiah et al., 2008; Norsa'adah et al., 2011; Cheng et al., 2015), diagnosed within 5.5 months (Norsa'adah et al., 2011) and underwent treatment within 1 month after diagnosis (Taib et al., 2007). Approximately, 31% of patients delayed presentation for more than 3 months (Ghazali et al., 2013) and 30-60% are reported to be diagnosed at late stage disease (Bhoo-Pathy et al., 2012; Ibrahim et al., 2012; Leong et al., 2007; Taib et al., 2011; Zainal Ariffin & Nor Saleha, 2011). As compared to the neighboring countries, Malaysian patients are diagnosed at later stages than Singaporean patients (Chang et al., 2011), which is similar to Thailand patients (Poum et al., 2014) but much earlier than Indonesian patients (Ng et al., 2011).

Malaysia is expected to increase the incidence of breast cancer due to the increasing life expectancy, better socio-economic status and changes in lifestyle (Cheng Har Yip et al., 2006). In addition to increasing incidence trends, women with breast cancer in Malaysia often delay and present with more advanced stages of disease. Therefore, further study should be done to assist clinicians and policy makers to improve strategies and implement better public health activities of breast cancer in the future and thus improving the cancer outcomes in Malaysia.

2.5 Biology of breast cancer

2.5.1 The formation of breast cancer

Breast cancer is a type of malignant tumor that develops from cells in the breast. The cancer cells grow when there is a mutation in somatic genes and then divide out of control, invading and damaging nearby tissues and organs. A cluster of cells dividing and growing over time for mutations and turn into atypical hyperplasia known as cancer (carcinoma). Cancer cells can break away from the original tumor and enter the bloodstream or lymphatic system and may spread to other parts of the body. The spreading of cancer cells to other tissues and organs occurs when the adhesion of these cancerous cells breaks down and spreads to new locations or known as metastasis.

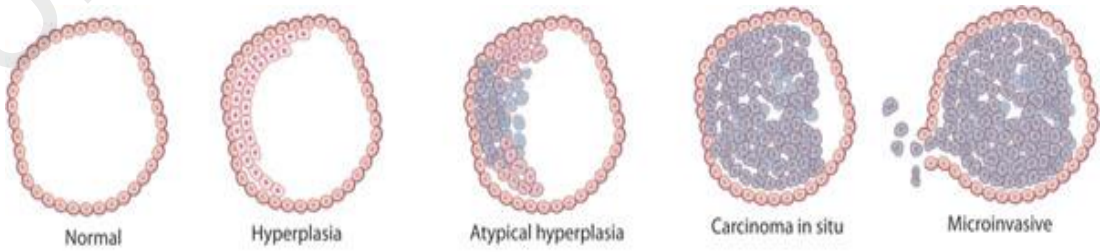


Figure 2.5: Microevolution of a cancer cell

(Source: http://www.nature.com/scitable/content/microevolution-of-a-cancer-cell-14707728. Accessed online on 20 September 2016)

2.5.2 Breast cancer symptoms

Breast cancer symptoms can be divided to asymptomatic and symptomatic disease. Asymptomatic breast cancer is detected through mammography screening while symptomatic breast cancer is detected through signs and symptoms, by which lump detection is the commonest noticeable symptom (Dahlui et al., 2013). More than 80% of breast cases are discovered after the women recognizing a lump (Quaife et al., 2014). Indications of symptomatic breast cancer other than lump may include changes in breast (larger, lower), nipple changing (position, shape, inverted, discharge), skin changing (dimpling, puckering, dimpling, rashness), constant pain in part of the breast or armpit, and swelling beneath the armpit or around the collarbone. Although pain is an unreliable tool in determining the presence or absence of breast cancer, it may be indicative of other breast health issues (American Cancer Society, 2014).

2.6 Management guidelines for breast cancer in Malaysia

2.6.1 Management of breast cancer

The guidelines for the management of breast cancer in Malaysia is based on the Clinical Practice Guidelines (CPG); Management of breast cancer ($2^{nd\ ed.}$) (Ministry of Health Malaysia, 2010). These guidelines are meant to guide clinical practice, based on the best available evidence at the time of development. Every health care provider is responsible for the management of a patient based on the clinical picture presented by the patient and the management options available locally.

2.6.2 Screening on general population

There are three main activities for breast cancer screening in Malaysia; Breast Self-Examination (BSE), Clinical Breast Examination (CBE) and mammography screening (Dahlui et al., 2011). A study conducted in five rural districts in Perak reported the uptake

of breast self-examination (BSE), clinical breast examination (CBE) and mammogram were 59%, 51% and 6.8%, respectively (Dahlui et al., 2013). The prevalence rate for breast examination was higher for the age group between 30-34 years old (82.04%) shows that breast screening facilities in Malaysia is still underutilized, especially by the target groups of 40 years and above (Dahlui et al., 2011).

Reference is made to the Clinical Practice Guideline (CPG) for breast cancer, whereby mammography is the primary method for breast cancer screening in Malaysia (Ministry of Health Malaysia, 2010). Clinical breast examination (CBE) and breast self-examination (BSE) are recommended to raise awareness instead of it as a screening method (Ministry of Health Malaysia, 2010), due to ineffectiveness in reducing breast cancer mortality (Kosters et al., 2008) and the effectiveness is equivocal (Thistlethwaite et al., 2007). However, a recent study in India showed that CBE reduces cancer stage (Sankaranarayanan et al., 2011). Thus, an update to this guideline is needed.

To encourage women to undergo mammogram screening for early detection of breast cancer, in year 2007 the Ministry of Women Family and Community Development (MWFC) has launched a program to subsidise the medical fees for every mammogram done in private clinics and hospitals registered with the National Population and Family Development Board Malaysia (NPFDB) or known as Lembaga Penduduk dan Pembangunan Keluarga Negara (LPPKN). Women aged 40-70 years are entitled to a subsidy of RM100 if the household income is RM5,000 and below, while subsidy of RM50 if the household income is RM5,000 and above (LPPKN, 2014). However, women aged 35-39 years who have a family history of breast cancer can also get this subsidy after being examined by a doctor (LPPKN, 2014). From this program, 18,000 women were screened, where 63 women (0.36%) were tested positive for breast cancer, while 1,543 women (8.9%) went for further investigation for breast cancer (LPPKN, 2014).

2.6.3 Referral to diagnostic centre

Assessment should be done by the referring doctors based on certain criteria, which may be useful to categorize patients into urgent and non-urgent cases. The criteria for early referral or urgent cases are women aged more than 40 years old presenting with a breast lump, lump size more than 3 cm in diameter and show clinical signs of malignancy (Ministry of Health Malaysia, 2010). However, there is no time frame was suggested in the CPG for referral time from the primary care to diagnostic centre. Furthermore, breast cancer should be detected in while the tumor is smaller, not until reaching a certain size or if there are overt signs of breast cancer.

2.6.4 Diagnosis of breast cancer

Triple assessment is an established method for diagnostic process for both symptomatic and asymptomatic women which consist of clinical examination, imaging (mammography and/or ultrasound) and biopsy (histology and/or cytology). Patients presenting with a breast symptoms should be evaluated with a full clinical examination, mammography and/or ultrasound followed by biopsy, either fine needle aspiration and/or core biopsy (Ministry of Health Malaysia, 2010).

Adjunct ultrasound to mammography improves breast cancer detection in women of all ages and should be offered to all symptomatic breast patients. Ultrasound should be used as an initial imaging modality for young women of 35 years and below. In patients presenting with clinically advanced breast cancer, further imaging modalities such as chest x-ray, liver ultrasound, and/or CT scan should be offered to assess the extent of the disease depending on the available resources (Ministry of Health Malaysia, 2010).

Fine needle aspiration cytology is considered as the initial method of pathological assessment for palpable breast lumps. Meanwhile, core biopsy may be used as a complement for pathological diagnosis if the fine needle aspiration cytology is equivocal

(Ministry of Health Malaysia, 2010). Histological confirmation should be obtained before any definitive surgical procedure is done.

2.6.5 Staging of breast cancer

Staging of breast cancer is the process to determine the extent of the cancer and is an important factor in determining the type of treatment. Cancer stages can be divided into early breast cancer (EBC), locally advanced breast cancer (LABC) and metastatic breast cancer (MBC) (AJCC, 2009). It is staged based on the size of the breast tumor (T), whether the cancer has reached nearby lymph nodes (N) and whether the cancer has metastasized (M), referring to the standardised American Joint Committee on Cancer (AJCC) staging system (AJCC, 2009). Once the T, N and M categories have been determined, the doctor will combine that information to find the cancer stage. Breast cancer is classified into subgroups and in aggregate gives the best staging profile for each patient (Edge et al., 2010).

2.6.6 Treatment of breast cancer

2.6.6.1 Surgery

The surgical management for women with breast cancer is based on the stages of disease. Surgery is the primary treatment for women with early breast cancer (EBC), either breast conserving surgery (BCS) or mastectomy (MAC) (Ministry of Health Malaysia, 2010). BCS is increasingly accepted as a surgical technique for breast cancer treatment but MAC is required if there are contraindications to BCS. Breast reconstruction after mastectomy should be discussed within the surgical team involved with the patient as to whether it should be carried out immediately or not.

Neo-adjuvant chemotherapy is an established option for most patients with locally advanced breast cancer (LABC). It can be offered to patients with operable LABC who are not suitable candidates for BCS at presentation. It is also offered to inoperable LABC

to downsize the tumour and enable subsequent surgery. For metastastic breast cancer (MBC), surgery of the primary tumour may be considered in selected cases (Ministry of Health Malaysia, 2010).

2.6.6.2 Oncology therapies

Adjuvant chemotherapy should be considered in all patients with early breast cancer (EBC) or women in pre-menopausal age with following risk factors; one or more positive axillary lymph nodes, ER negative, HER2 3+ disease, tumour size more than 2cm and grade 3 disease. However, neo-adjuvant chemotherapy should not be routinely given to patients with early breast cancer (Ministry of Health Malaysia, 2010).

Adjuvant radiotherapy should be offered to post-mastectomy patients with 4 or more lymph nodes or with positive margin. It also can be offered to post-mastectomy patients with 1 to 3 lymph nodes, node negative disease and T3 and T4 tumours. However, all patients with post-BCS should be offered adjuvant radiotherapy for both invasive breast cancer and ductal carcinoma in situ (Ministry of Health Malaysia, 2010).

Endocrine therapy has been demonstrated to benefit in only estrogen receptor (ER) positive cancer. Tamoxifen (Tmx) should be offered to all patients with ER positive early breast cancer, while aromatase inhibitors (AI) should be offered to post-menopausal patients with ER positive advanced breast cancer (Ministry of Health Malaysia, 2010).

2.7 Delays in breast cancer

2.7.1 Definition of delay

The term ‘delay’ in the cancer literature is used to refer to time delays and to denote advanced stage at presentation. The different terminologies used commonly results in some misperception to readers and future researchers. Some researchers have a tendency

to avoid use of the word delay, not only because of this confusion, but also because the term implies an active decision for inaction (Macleod et al., 2009). However, this term is used extensively in the literatures and as such is impossible to avoid in a report of this nature. Any reference to delay in this research is referring to the time delay.

2.7.2 Definition of breast cancer delay

The terminology of 'breast cancer delay' (BCD) as introduced by Pack & Gallo (1938) refers to the elapsed time between the symptoms discovery and the initiation of medical treatment. It looks for whole perspective from both aspects of patient and health system. Similar definition was also used for 'total delay' terminology by Bish et al. (2005).

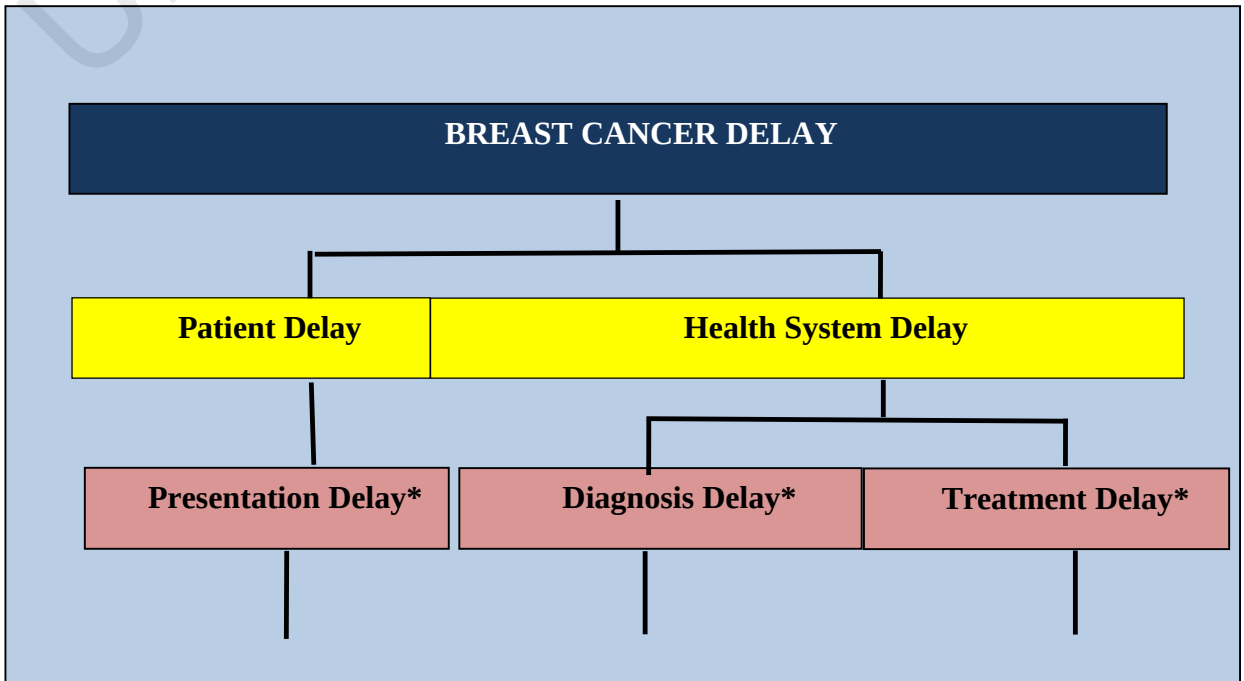
Breast cancer delay is divided into two categories which are 'patient delay' and 'system delay'. Patient delay is the delay in seeking medical attention after self-discovering a potential breast cancer symptom (Caplan, 2014). The interval is between the first symptoms discovery and medical consultation (Memon et al., 2013; Piñeros et al., 2009; Richards et al., 1999; Yurdakul et al., 2015; Unger-Saldaña & Infante-Castañeda, 2009). After a symptom is detected, the patient would evaluate whether the symptom is somewhat life-threatening which requires attention and then prompts her to present at primary care to obtains professional help (Andersen et al., 1995). The patients' awareness, knowledge, behavior and decision may influences the patient delay (Piñeros et al., 2009).

Meanwhile, system delay is the form of delay caused within the health care system and/or involving patients getting appointments, scheduling diagnostic tests, receiving a definitive diagnosis, and initiating therapy (Caplan, 2014; Taib et al., 2014). The interval is between the medical consultation and initial treatment (Bright et al., 2011; Crispo et al., 2009; Jassem et al., 2013; Unger-Saldaña et al., 2015). This interval is also known as provider delay (Unger-Saldaña & Infante-Castañeda, 2011), physician delay (Yurdakul

et al., 2015), diagnostic delay (Barber, Jack, & Dixon, 2004), clinical delay (Gorin, Heck, Cheng, & Smith, 2006) and treatment delay (Jung et al., 2011). Complex interaction between socio-cultural and current economics structure influences health care system and determine the time to referral, diagnostic resolution and treatment initiation (Bright et al., 2011).

In 2006, Gorin et al., (2006) separated system delay into 'diagnosis delay' and 'treatment delay'. This makes breast cancer delay divided into 3 intervals; presentation, diagnosis and treatment. Recently, the breast cancer delay interval is updated and transformed by Taib et al. (2014) into eight stages of delays; appraisal, disclosure, illness, behavioral/referral, scheduling, diagnostic, treatment decision and treatment.

In this study we used three measures of delay; presentation delay, diagnosis delay and treatment delay, whereby these three measures are suitable to demonstrate the time intervals of important time points in breast cancer journey. Furthermore, we can determine associated factors to delays amongst women with breast cancer in Malaysia. Figure 2.6 indicates the measures of breast cancer delay.



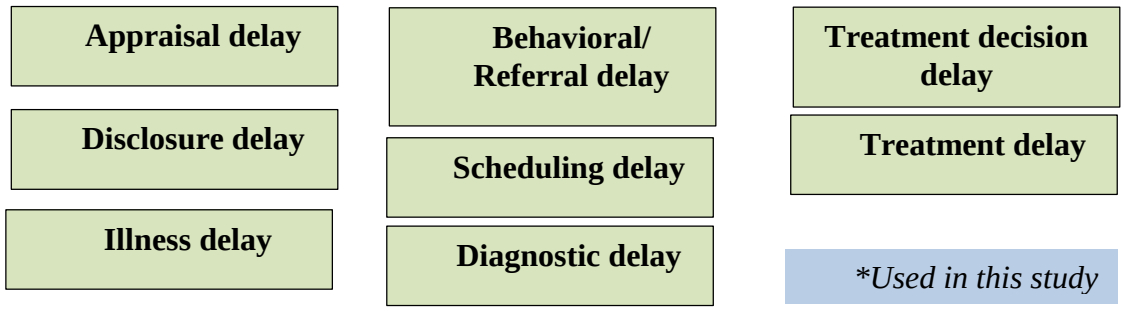


Figure 2.6: Terminologies of breast cancer delays

2.8 Breast cancer delay model

2.8.1 Three stages of total delay model

Many studies have defined breast cancer delay in the literature and generate numerous models for deeper understanding, thus making comparisons problematical. The first breast cancer delay model is known as 'three stages of total delay' (Fig. 2.5) which was generated by Safer (1979). The model has defined three stages of delay; appraisal, illness and utilization delay. However, the model was described only on the patient aspects.

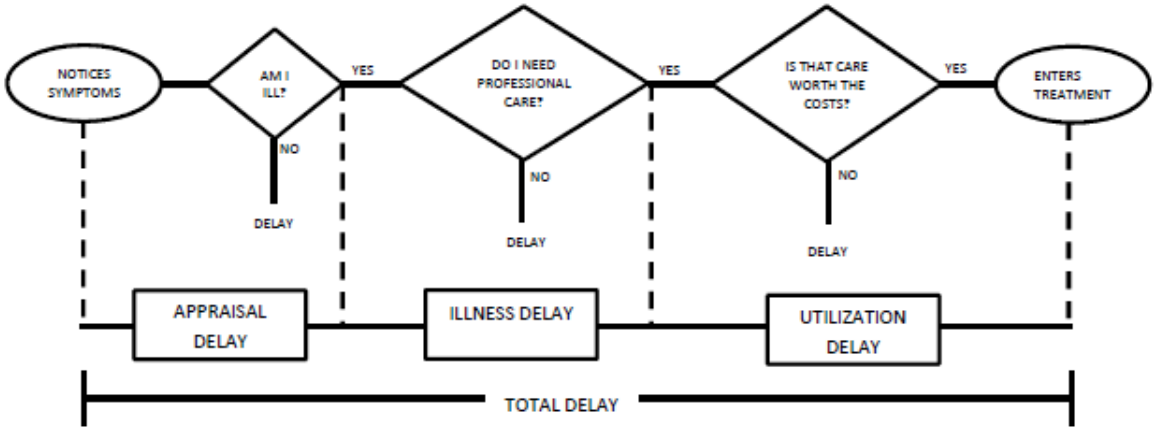


Figure 2.7: The three stage of total delay

Source: Reprinted from "Determinants of three stages of delay in seeking care at a medical clinic" Safer, M A., Tharps, Q.J., Jackson, T.C, & Leventhal, H., 1979 in *Med Care,17(1), pg.11-29.*

2.8.2 The total patient delay model

The model was then updated by Andersen et al. (1995) and is further divided into five stages of delay; appraisal, illness, behavioral, scheduling and treatment, which is known as the 'total patient delay' (Fig. 2.6). It is described briefly on the patient and system delay, whereby it includes treatment delay which attributed more towards in-hospital care. These stages of delay are found to be independent of each other.

Appraisal delay is found to be the major stage of the total delay. The pre-diagnostic patient delay is very well described. However, post-diagnostic patient delay is not well elaborated in basic terms. Post-diagnostic delay is the time after diagnosis before patients begins and completes the recommended treatments. The patients' decision

making process on treatment with regards to adherence on the recommended treatment occurs during this period, gives impact in the post-diagnostic period. Therefore, this study recommends further research must be done to define post-diagnostic delay.

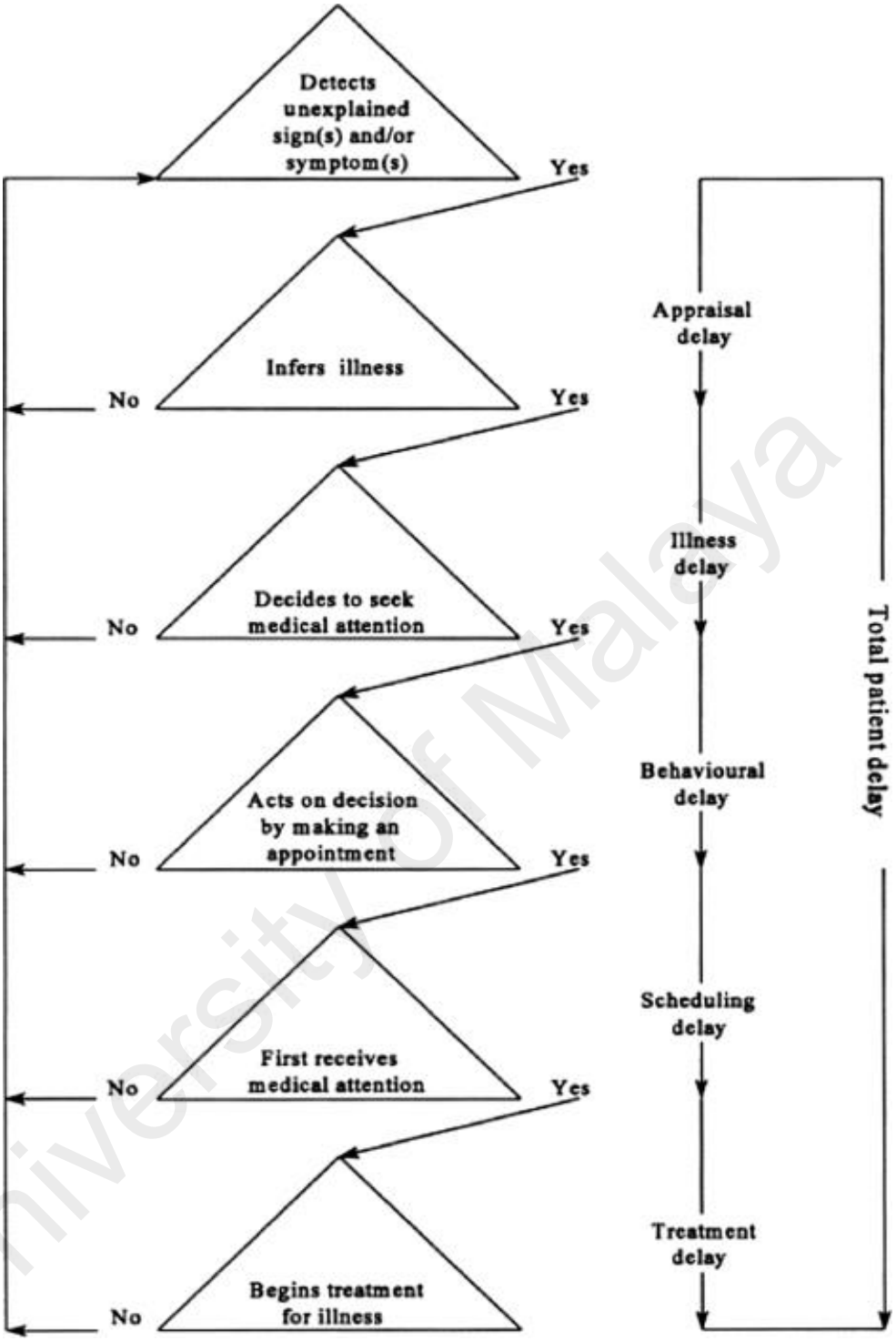


Figure 2.8: The total patient delay model

Source: Reprinted from "Delay in seeking a cancer diagnosis: Delay stages and psychophysiological comparison processes" by B.L Anderson & J.T Cacioppo, 1995 in *British Journal of Social Psychology, pg.35.*

2.8.3 The total breast cancer delay model

The breast cancer delay model was later updated and transformed as the 'total breast cancer delay' (Fig. 2.7) by Taib et al. (2014) with additional three stages of delay. There are eight stages of breast cancer delays in this model which is divided into appraisal delay, disclosure delay, illness delay, behavioral/referral delay, scheduling delay, diagnostic delay, treatment decision delay and treatment delay. This model was generated to understand where the delay begins specifically in the Malaysian population. Each delay point may occur due to the patient and/or system, thereby contributed to the construction of the patients and system decision making.

The breast cancer delay model covers the length of the period beginning from the symptom recognition up to receiving initial treatment. It is generally divided into two types of delay; 'patient delay' and 'patient and/or system delay'. Patient delay is referring to the delay between symptom discovery and first medical consultation. This period has been considered to be the patient's responsibility. Meanwhile, patients and/or system delay are referring to the delay between first medical consultations until receiving definitive treatment which considered being the patient's and/or system responsibility. Different people will delay at different points in the process and the different symptoms and conditions will also bring about different patterns of response. Therefore, breast cancer patients may experience delays in one or more points of delay.

Health care services in Malaysia induce active competitions between conventional and alternative health care systems. It begins before diagnosis and continues until the treatment decision period. Understanding the importance of both systems may guide policy makers to regulate its practices in the community. With the providing framework, this model gives a view to the points of delay and provides a framework for researchers to understand the patient's journey in breast cancer. These points are also useful for policy

makers in measuring the health care performance. Thus, it would help in designing interventions and enabling earlier presentation, diagnosis and treatment in the future.

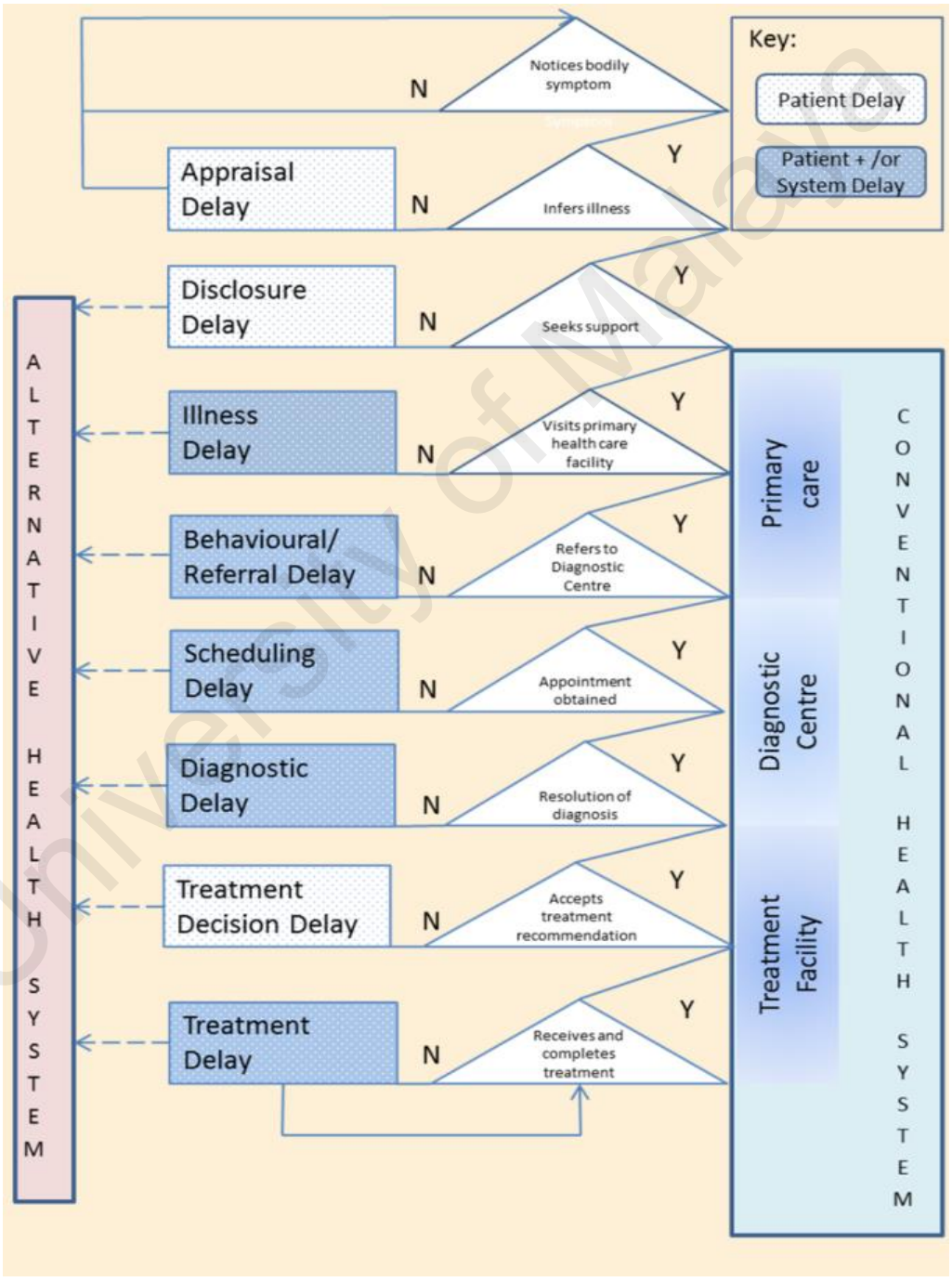


Figure 2.9: The Total Breast Cancer Delay Model (TBCD)

Source: Reprinted from "A grounded explanation of why women present with advanced breast cancer" by N.A.Taib, C.H.Yip & W.Y.Low, 2013 in *World Journal of Surgery, pg.1681*.

2.9 Presentation delay

2.9.1 Definition of presentation delay

'Presentation delay' is defined as time taken from the symptoms discovery to the first presentation at primary care provider (Lim et al., 2015; Facione & Facione, 2006; Ghazali et al., 2013; Harirchi et al., 2005; Norsa'adah et al., 2011; Unger-Saldaña & Infante-Castañeda, 2009; Montazeri et al., 2003). The time taken to presentation begins from the first discovery of symptoms, followed by seeking for help and support, and ends with the first visit to a primary health care facility (Taib et al., 2014). The time interval refers to a lag of time in the presentation of self-discovered or symptomatic cancer symptoms which is an individual's first awareness of symptoms to the first visit at primary care facility for initial medical consultation. This period has been considered to be the patient's responsibility as the time period between symptom discovery and the first medical consultation is affected by the patients' decision making. Referring to the Total Breast Cancer Delay (TBCD) model, presentation delay is a combination of three stages of delays; appraisal delay, disclosure delay and illness delay (Taib et al., 2014).

Appraisal is a process of symptom interpretation and was found to be the major stage, accounting to 60% of the presentation delay (Andersen et al., 1995). It occurs when there is a failure to recognize any bodily changes and to classify it as a serious condition. This process is determined by knowledge of the disease and symptoms, the need to disclose for social support and recognition the presence of the breast symptoms (Taib et al., 2014).

Meanwhile, disclosure delay is defined as a failure to disclose the symptoms when there are suspicions of cancer (Taib et al., 2014). Disclosure delay occurrs when there is

social isolation. Therefore, disclosure is seen as an important way to receive support and obtain help in seeking for breast cancer treatment. The social network is usually the first place where individuals seek advice to make sense of their symptoms and decide the course of action, although social relations are not always supportive and can be negative (Rastad et al., 2012). Informational support, instrumental support, emotional support and decision-making support are crucial for manifestation of the initial medical contact as well as for the continuity of care (Unger-Saldaña & Infante-Castañeda, 2011).

Illness delay is defined as a failure to make an appointment or initial medical contact after symptom recognition (Taib et al., 2014). It begins from the time an individual concludes that she is ill and present herself at primary care provider for initial medical consultation (Andersen et al., 1995). At this stage, that individual will determine the decision to seek medical attention either to the aid of conventional or alternative health system (Unger-Saldaña & Infante-Castañeda, 2011). The decisions regarding the sources of care and timing of utilization are also shaped by the characteristic of the local cultural and social context (Abdullah et al., 2013).

2.9.2 Cut-off points of presentation delay

The cut-off points are different as each researcher used different measurement points for measuring delays. There is no standardized measurement for presentation delay. However, based on numerous studies in Malaysia (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011), Asia (Ali et al., 2008; Harirchi et al., 2005; Ibrahim & Oludara, 2012; Khan et al., 2015; Memon et al., 2013; Mody et al., 2013; Montazeri et al., 2003; Pakseresht et al., 2014; Poum et al., 2014) and western countries (Bish et al., 2005; Piñeros et al., 2009; Jassem et al., 2013; Ruddy et al., 2014), 3 months period has been used as cut-off point for the time taken from symptom discovery to first presentation of medical consultation. This delay is commonly indicated by the length of symptom

encountered by the patients. The cut-off point is based on the evidence that patients who delay presentation for 3 months or more have lower 5-year survival rates than those with less delay (Richards et al., 1999).

Other measurements to indicate this delay are 2 weeks (Taib et al., 2007), 2 months (Rajan et al., 2011) and 6 months (Galukande, 2014) which varies across studies due to the patients' socio-demographic and pathology differences.

2.9.3 Proportion of presentation delay

Delay in presentation is common among women with breast cancer in Malaysia (Taib et al., 2007). It is reported that Malaysian patients sought treatment from 0 to 11 years (Norsa'adah et al., 2011) with a median of 2 to 4 months after symptoms discovery (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011; Taib et al., 2007; Yip et al., 2006). The prevalence of delayed presentation by more than 3 months ranged from 33-59% in Malaysia (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011).

In Asian studies, patients in Thailand showed a shorter median time to presentation of 12 days (Poum et al., 2014) compared to Indonesian and Hong Kong patients with respective median of 90 days (Norleli et al., 2014) and 13 weeks (Yau et al., 2010). High prevalence of presentation delay was also found in other Asian countries such as 17% in Thailand (Poum et al., 2014), 29% in Hong Kong (Yau et al., 2010), 25-42.5% in Iran (Montazeri et al., 2003; Harirchi et al., 2005), 39-42% in Pakistan (Khan et al., 2015; Memon et al., 2013) and 53.9-61.6% in India (Ali et al., 2008; Pakseresht et al., 2014b). The highest incidence of presentation delay is found amongst African patients with 85% in Rwanda (Mody et al., 2013), 81.6% in Nigeria (Ibrahim & Oludara, 2012) and 80% in Uganda (Galukande, 2014).

Although there is higher incidence of breast cancer in Western countries, the patients typically present early for medical consultation compared to Asian patients. A study in London revealed that only 19% of breast cancer patients reported delays of more than 3 months (Burgess et al. 1998). This figure is similar to a study in United States where 17% delayed presentation more than 2 weeks after symptom discovery (Ruddy et al., 2014). In addition, lowest percentage of presentation delay is reported in United Kingdom with 8.2% present to the family physician after 2 weeks (Quaife et al., 2014). The shorter presentation delay in developed countries is probably caused by increased public awareness of symptom appraisal and cultural openness about breast cancer in general (Bairati, Jobin, Fillion, Larochelle, & Vincent, 2007).

2.9.4 Factors associated with presentation delay

There are three main factors namely personal, economic and sociocultural factors which have been proposed in a systematic review to affect patient delay in presenting and getting initial cancer treatments (Sharma et al., 2012). Personal factors include age, ethnicity, education, marital status, family history and clinical presentation of breast cancer. Fear of medical treatment costs, lesser income status and financial issues are seen under economic factors (Lim et al., 2015; Sharma et al., 2013). While breast cancer awareness, alternative therapy use, fear, denial, anxiety and stigma of disease are classified under sociocultural factors (Sharma et al., 2013).

Clinical presentation of breast lumps is found to be the most significant determinant for both patient and provider delay (Khan et al., 2015). Breast lump is significantly a sign of illness and failure to initially recognize this symptom leads patients to delay presentation (Bish et al., 2005).

Strong evidence has found that older age is associated with presentation delay (Arndt et al., 2002). Those who delayed presentation are older (Bish et al., 2005; Harirchi

et al., 2005; Piñeros et al., 2009) with patients over 65 years of age tended to have longer duration of symptoms (Richards et al., 1999). Older women are poor at identifying symptoms, perceived to face less personal risk of developing disease than younger women, has more negative beliefs, has more disabilities, fear of disfigurement and adverse economic situation are proposed as the reason for delayed help seeking behavior among older women (Bish et al., 2005).

Race and ethnicity are associated in presentation delay with longer delays time in black patients than white patients in United State (Caplan et al., 2000) and more Malay patients delayed help-seeking compared to Chinese and Indian patients in Malaysia and Singapore (Lim et al., 2015). However, a study in Malaysia found Chinese ethnicity delayed longer than Indian ethnicity due to high complementary and alternative use (Ghazali et al., 2013). In contrast, another study in a multiethnic settings have found no difference between patients delay of different ethnics in public hospitals setting (Norsa'adah et al., 2011).

Patients with low educational background are more likely to have longer duration of symptoms prior to seeking medical treatment in several studies (Ali et al., 2008; Crispo et al., 2009; Facione & Facione, 2006; Harirchi et al., 2005; Montazeri et al., 2003). Besides that, marital status is related to patient delay with single women being more likely to delay presentation than married women (Ibrahim & Oludara, 2012; Memon et al., 2013; Norleli et al., 2014). More delays are reported among divorced/widowed women than married women (Ali et al., 2008; Ghazali et al., 2013; Montazeri et al., 2003). These findings indicate that there are lack of motivation in seeking help and less support among single and divorced/widowed women (Facione 1993). In contrast, another study found that married women delay more as compared to unmarried women due to multiple roles

and duty (Harirchi et al., 2005), while another study reported no association between marital status and patient delays (Ramirez et al., 1999).

Socioeconomic status plays at major role in delay presentation. Late presenters belonged to the lower socioeconomic group in Pakistan and most of them placed poverty as the main reason for delay in presentation (Harirchi et al., 2005; Sharma et al., 2012). Similarly, low income black patients have been reported to delay consultation compared to white patients in US (Facione & Facione, 2006) but none of the other socio-economic factors is significantly associated with patient delay in Germany (Arndt & Stu, 2002).

Unavailability of health care services in rural areas and embarrassment of discussing breast issues were seen in low socioeconomic status groups which are the barriers to access and adherence to cancer treatments (Forbes et al., 2014; Norleli et al., 2014; Mohaghegh et al., 2015). Meanwhile, lack of insurance, geographic, linguistic and cultural barriers, are associated with delays in seeking treatment among low socioeconomic status in developed countries (Arndt & Stu, 2002; Innos et al., 2013).

Delayed presentation is commonly associated to the strong belief in traditional or alternative medicine, negative social-cultural perception of the disease, and coupled with fear and denial (Taib et al., 2011). Fear of abandonment by husbands and competing roles of being a mother and wife are cited reasons for delay among Malaysian patients (Norsa'adah et al., 2012). Further to that, embarrassment of exposing their breasts and lack of psychosocial network and support contributed to presentation delays in Thailand patients (Thongsukai et al. 2000).

Studies have found that poor geographical access due to isolation of rural areas and longer travel time to hospital contributed to patient delay (Poum et al., 2014). This is similar to a study in France, where poor geographical access to primary health care

significantly increased the risk of delay (Molinié et al., 2013). Geographic information system (GIS) can be used to evaluate the location of existing health facilities, the accessibility and associated utilization of health care services with the structure of disease patterns in a population (Moore and Carpenter, 1999).

2.10 Diagnosis delay

2.10.1 Definition of diagnosis delay

'Diagnosis delay' is defined as time taken from the first presentation at primary care provider to a diagnostic resolution (Bairati et al., 2007; Ermiah et al., 2012; Huo et al., 2014; Plotogea et al., 2014; Pruitt et al., 2014; Samphao et al., 2009; S. H. Shieh et al., 2013). Time taken for diagnosis begins from the first presentation to referral at a diagnostic centre, followed by biopsy, pathology report and disclosure of diagnosis (Taib et al., 2014). The time interval refers to a lag of time of referral from the primary care provider to the diagnostic centre, followed by obtaining for diagnostic examination appointment and disclosure of histopathological diagnosis of breast cancer (Gorin et al., 2006). This period has been considered to be the patient's and/or health system responsibility by which the time period between first presentation and the diagnostic resolution is affected by the patients' decision and health system. Referring to the Total Breast Cancer Delay (TBCD) model (Taib et al., 2014), diagnosis delay is a combination of three stages of referral delay, scheduling delay and diagnostic delay (Taib et al., 2014).

Referral delay is a process of referring patients from primary care provider to the diagnostic center (Taib, 2012). Referral systems are seen in place with health centres referring to surgical outpatient services, primary care physicians within the same hospitals as well as the cross hospitals references. In addition, behavioral delay occurs when the patient refuses medical check-up although she is referred for further diagnostic

investigations (Bish et al., 2005). Time is spent between the decision to seek medical attention and the person acting on this decision (Andersen et al., 1995).

Scheduling delay occurs due to the failure to obtain an appointment in the diagnostic centres within the conventional health system (Taib, 2012). Usually, patients with symptom are seen in primary care clinics are referred to diagnostic centres (e.g. surgical outpatient clinics or breast clinic) for diagnosis. Navigating patient to the right diagnostic facility is important to obtain a timely diagnosis.

Diagnostic delay is an elapsed time between diagnostic centre appointment and receipt of histopathology diagnosis of breast cancer (Maly et al., 2011). The diagnostic process includes visiting the diagnostic centre, scheduling or referring for investigations, adhering to diagnostic investigations and receipt of histopathology diagnosis (Taib, 2012). All women with symptom require triple assessment to minimize delay in diagnosis of breast cancer (Barber et al., 2004).

2.10.2 Cut-off points of diagnosis delay

The cut-off points vary as researchers use different measurement points for measuring diagnosis delays. There is no standardized measurement for diagnosis delay. However, based on numerous studies in Asia (Ermiah et al., 2012; Huo et al., 2014; Shieh et al., 2014) and western countries (Bairati et al., 2007; Plotogea et al., 2014), 1 month or 30 days has been used as a cut-off point for the time taken from first presentation to diagnostic resolution. This delay is commonly indicated by the length of referral, investigations and histopathology results for diagnosis resolution and contributed by both the patients and/or the health care system (Taib et al., 2014).

Other cut-off points found are 2 months (Caplan et al., 2000; Maly et al., 2011; Rajan et al., 2011), 3 months (Al-Amri, 2015; Poum et al., 2014; Ruddy et al., 2014;

Norsa'adah et al., 2011; Facione & Facione, 2006; Burgess et al., 1998; Pack & Gallo, 1938;) and 6 months (Soares et al., 2012). The definition of diagnosis delay varies widely as some studies included time from the point of symptoms discovery not after the initial visit to a diagnostic centre.

2.10.3 Proportion of diagnosis delay

The median time for breast cancer diagnosis in Malaysia varies from 9 days after presentation in urban hospitals in Kuala Lumpur (Lim et al., 2014) and 5.5 months after symptoms discovery (Norsa'adah et al., 2011). Approximately, 72.6% of women in East coast of Malaysia has delayed diagnosis of more than 3 months and 45.5% has delayed diagnosis of more than 6 months (Norsa'adah et al., 2011). The diagnosis interval discrepancy could be due to differing measurement points, screening practices, health seeking behavior, patient compliance and health resources available in an health care institution (Taib et al., 2007).

Few studies on diagnosis delay are conducted in the Asian setting. There is a high proportion of diagnosis delay in 42% in Thailand (Poum et al., 2014), 60.7% in China (Huo et al., 2014) and 70% in Libya (Ermiah et al., 2012). Patients in Thailand, Singapore and Libya showed a median diagnosis time of 21 days, 65 days and 7.5 months respectively (Ermiah et al., 2012; Poum et al., 2014; Sy et al., 2015). Meanwhile, patients in Taiwan reported a lower proportion of 9.7% delay with a median of 28 days (Shieh et al., 2014). The proportion of diagnosis delay varies across Asian studies due to the different study methods.

Meanwhile, shorter median diagnosis time of 16 to 32 days is seen in the US (Caplan et al., 2000; Ruddy et al., 2014) and 31 days in Canada (Plotogea et al., 2014). Approximately, 48.7% has delayed diagnosis of more than 5 weeks in Canada (Bairati et al., 2007), 51.4% of more than 2 months, 12% of more than 3 months in the US (Ruddy

et al., 2014) and 42.7% of more than 6 months in Brazil (Soares et al., 2012). The literature suggested that 5 weeks to 2 months is the suitable time intervals for breast cancer diagnosis (Olivotto et al. 1999;Gwyn et al., 2004; Bairati et al., 2007). According to Ruddy et al. (2014) most of family physicians in the US refer patients directly to hospitals after their first visit Approximately, 83 to 90% are referred to hospital within 4 weeks after presented to a GP (Burgess et al., 1998; Jones et al., 2014). Small proportion of 6% to 16% experienced referral delays of more than 3 months (Macleod et al., 2009; Mccain, Newell, Badger, Kennedy, & Kirk, 2011; O'Rourke, 2012). Efforts to reduce diagnosis waiting time have been emphasized in United Kingdom, concentrating on referral to diagnostic centers within 2 weeks (Ireland National Cancer Registry, 2012; Mccain et al., 2011). However, no consensus or standardized timeframe for breast cancer diagnosis has been applied in Malaysia and other Asian countries.

2.10.4 Factors associated with diagnosis delay

The factors significantly associated with diagnosis delay in Malaysia are the use of alternative therapy, presence of breast ulcer, palpable axillary lymph nodes, non-cancer interpretation and a negative attitude toward treatment by the patients and false-negative diagnostic test by the health system (Norsa'adah et al., 2011). In Malaysia, development of breast clinics throughout the country has been stagnant due to lack of resources, manpower and specialties in every aspects (Yip et al., 2014). Thus, the problems in providing a comprehensive service for breast cancer diagnosis in Malaysia may explain to this delay (Yip et al., 2014).

Other Asian studies had reported that lower service level of first visit and number of hospital visit (Huo et al., 2014; Shieh et al., 2014) are the factors for diagnostic delay by the health system. The additional visits, failure to recognize cancer symptoms and poor

management of where to refer the patient by the health care provider are barriers for prompt reference (Pace, Mpunga, & Hategekimana, 2015).

Furthermore, lack of competence amongst general practitioner, overreliance of mammogram and pathologic findings, inability to obtain conclusive results on fine needle aspiration and misdiagnosis have been reported as factors caused by health systems for diagnostic delay (Bairati et al., 2007; Baliski et al., 2014; Barber et al., 2004; Burgess et al., 1998; Taib et al., 2014) and women having a surgical biopsy had a greater delay diagnosis than needle biopsy (Plotogea et al. (2014). Moreover, provider and the health care system are said to be responsible for the 45% delay cases in the US through difficulties in scheduling or physician inaction (Caplan et al., 1996).

Longer referral time is found to be a reason of diagnostic delay. However, referral process is not related to the health care system alone, but also linked with the decision-making process by the patients (Macleod et al., 2009; Mccain et al., 2011; Pace et al., 2015). Patient might not attend to the diagnostic center when they decided to ignore the symptoms during the period of referral (Yu et al., 2015), poor communication between patients and doctors, over reliance on family decision and negative beliefs of cancer (Norsa'adah et al., 2012; Taib et al., 2014; Taib et al., 2011). These factors would lengthen the referral interval and indirectly affect the diagnosis outcome.

2.11 Treatment delay

2.11.1 Definition of treatment delay

'Treatment delay' is defined as time taken from the receipt of diagnostic resolution to the initial treatment (Caplan et al., 2000). Referring to the Total Breast Cancer Delay

Model (TBCD), treatment delay is a combination of two stages of treatment decision delay and treatment delay (Taib et al., 2014).

Treatment decision delay occurs when treatment recommendations are not adhered to by the patient. Patient plays a large role in decision making, but social contacts influences responses of the patient and can lead towards decision delay. Meanwhile, treatment delay is mainly a health systems failure of failing to provide treatment services in a timely and effective manner. Losing patients to follow-up and not recommending effective treatment in a timely fashion are health system failures.

2.11.2 Cut-off points of treatment delay

Treatment delay is defined as the time duration between the histological diagnoses to initiation of treatment. The Clinical Practice Guidelines (CPG) on management of breast cancer has recommended that breast cancer patients in Malaysia should receive initial treatment within 2 months of presentation (Ministry of Health Malaysia, 2010). Meanwhile, previous study suggested that 1 month or 30 days is an adequate time for the physician to take appropriate action after diagnosis resolution (Caplan et al., 2000; Pack & Gallo, 1938; Pérez et al., 2008; Rastad et al., 2012; Sainsbury et al., 1999; Shandiz et al., 2012; Molinié et al., 2013). Other studies suggested that patients should be treated within 43 days (Samur et al., 2002), 5 weeks (Bairati et al., 2007), 60 days (Connors et al., 2014) after initial biopsy and within 3 months after diagnosis (Jung et al., 2011; Seneviratne et al., 2014; Yau et al., 2010). In addition, 31 days is the standard cancer waiting time for treatment delay on the UK's National Health Service target in the year 2000 (Sharpe et al., 2008).

The cut-off points for treatment delay are among the studies although some studies had reported on the time interval of breast cancer delay. There is no consensus or

standardized measurement of an acceptable duration for treatment after the histological diagnosis of breast cancer.

2.11.3 Proportion of treatment delay

The median time from diagnosis to initial treatment of breast cancer in a university hospital in Kuala Lumpur ranged from 18 to 19 days (Mujar et al., 2013; Yip et al., 2011) and longer median of 1.2 months seen in Kelantan (Norsa'adah et al., 2012). Meanwhile, the median time taken from diagnosis to surgery, chemotherapy, radiotherapy and hormonal therapy in 8 urban medical centres are 11 days, 51 days, 194 days and 171 days respectively (Lim et al., 2014). It is also found that 21.9% of breast cancer patients in a university hospital had treatment delay of more than 1 month after diagnosis (Mujar et al., 2013).

Studies in Asia reported the median values for time to initial treatment is 15 days to 22 weeks (Samur et al., 2002; Shandiz et al., 2012; Yau et al., 2010), while the median time from diagnosis to surgery and chemotherapy are 7.5 days and 34.5 days respectively (Samur et al., 2002). In addition, 29% of patients experienced treatment delays exceeding 12 weeks as reported from a study in Hong Kong (Yau et al., 2010).

Shorter median time taken to treatment is seen in other western studies. It is reported that the median interval from diagnosis to treatment is between 10 to 45 days (Brazda et al., 2010; Caplan et al., 2000; Connors et al., 2014; Pérez et al., 2008; Plotogea et al., 2013; Sasha et al., 2013). In contrast, longer median time to treatment is seen in Poland (11 weeks) (Jassem et al., 2013). In addition, the median waiting times from final surgery to postoperative chemotherapy and postoperative radiotherapy is between 44 days and 75 days respectively (Plotogea et al., 2013).

Interval from diagnosis to treatment of breast cancer is longer at general hospital than a university hospital with 53 days versus 33 days respectively (Brazda et al., 2010). Furthermore, the time to treatment significantly increased over the study time period of year 1998, 2003 and 2008, with mean duration of 21.8 days, 31.3 days and 41.1 days respectively (Hulvat et al., 2010). Besides, patients who had an MRI had a longer median time to treatment of 43 days than 32 days for those who did not use MRI (Hulvat et al., 2010).

2.11.4 Factors associated with treatment delay

Treatment delay is generally thought to affect patients' prognosis. Early treatment is important as delay is preventable and can lead to improved survival (Smith et al., 2013; You et al., 2015). Ethnicity is significantly associated with delaying treatment amongst breast cancer patients in Malaysia (Mujar et al., 2013) as seen in other studies (Bustami et al., 2014; Caplan et al., 2000; Sasha et al., 2013). Malay ethnicity has 1.9 odds of delayed treatment compared to the Chinese (Mujar et al., 2013). Another factor found in a qualitative study was treatment decision delay where patient factors contributed towards delays in treatment (Taib et al., 2014).

Furthermore, late stage disease is associated with longer time to treatment amongst breast cancer patients (Rastad et al., 2012). However, an inverse relationship between stage and time to treatment are seen (Pérez et al., 2008; Plotogea et al., 2013) or found that delay in treatment do not affect prognosis (Connors et al., 2014; Mujar et al., 2013). Although the relationship between cancer stage and treatment delay remains controversial, there is considerable evidence that treatment delay cause psychological distress and decreased quality of life in patients (Latarche C et al., 2004).

In addition, lack of awareness and knowledge, cancer beliefs, treatment beliefs, financial problems, emotional burden, severe side effects, paternalistic style of

communication, unmet information needs, longer patient delay times and higher levels of distrust are the significant factors towards treatment delay contributed by patient factors (Caplan et al., 2000; Plotogea et al., 2013; Rastad et al., 2012; Shandiz et al., 2012). Meanwhile, hospital type, public sector treatment, mastectomy, earlier year of diagnosis and elective admission are the significant factors for treatment delay contributed by health care systems (Bustami et al., 2014; Jassem et al., 2013; Pérez et al., 2008; Yau et al., 2010).

2.12 Adherence to breast cancer treatments

2.12.1 Definition of adherence

The term *adherence* is commonly used in recent literature (Aalto, 2013; Adisa et al., 2008; Courneya et al., 2008; Kirk & Hudis, 2008; Schwentner et al., 2013; S. Seneviratne et al., 2015; Steve, 2008). Adherence is defined as the extent to which a person's decision and behavior corresponds with medical or health advice (Osterberg & Blaschke, 2005). Many health care providers prefer the word *adherence*, because *compliance* suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on an established therapeutic agreement between the patient and the physician (Adisa et al., 2008; Steve, 2008).

The role of breast cancer treatments like surgery, chemotherapy, radiotherapy and hormonal therapy in reducing recurrence and death in breast cancer patients has been established (Brito et al., 2014). However, there is limited source of published literature on adherence to breast cancer treatments in Malaysia. Clinical trials have clearly demonstrated the benefits of treatment in women with breast cancer but little is known on how this treatment is actually used in the general population.

2.12.2 Proportion of non-adherence to breast cancer treatments

Several studies have been conducted on breast cancer treatment adherence in Malaysia. Breast cancer surgery is found to be highly accessible in Malaysia with 88.3-89% of patients having surgery (Lim et al., 2014; Mujar et al., 2013). The non-adherence rate for chemotherapy, radiotherapy and hormonal therapy are reported as 38%, 38% and 43% respectively and access to Trastuzumab is limited in Malaysian cancer care due to the high cost and inadequate public funding (Lim et al., 2014).

Non-adherence to breast cancer treatments are seen in other countries. A study on non-adherence for chemotherapy in Nigeria is over 80%. Fewer patients are seen to default after the first chemotherapy cycle but approximately half (50.5%) of patients defaulted after the third cycle (Adisa et al., 2008). However, less percentage is seen in developed country where only 43% of patients did not adhere to chemotherapy in New York, US (Lebovits, 2015).

Meanwhile, the proportion of women who did not adhere to hormone therapy is reported to be between 16.4-23.7%. However, this is based on different study methods (Brito et al., 2014; Kirk & Hudis, 2008). The non-adherence rate for Tamoxifen increased over time, where non-adherence rates for the first, second, third, fourth and fifth year of hormonal therapy were 23.2%, 26.5%, 28.6%, 33.7% and 40.7% (Seneviratne et al., 2015). Similarly, 13% did not take tamoxifen in the first year and increased to 50% by the fourth year of therapy (Partridge et al., 2003).

2.12.3 Factors associated with non-adherence to breast cancer treatment

Barriers and predictors to non-adherence to treatment depend on many co-existing factors. Patient adherence to a long-term intervention depends on the patient's view of the benefits, risks, and cost of the intervention. Postulated reasons for non-adherence amongst breast cancer patients in Malaysia are; patients refusing treatment, seeking care

in another centre and relying on alternative or traditional treatment (Chui et al., 2014; Chui et al., 2015; Leong et al., 2007; Lim et al., 2014).

Ethnicity is associated with non-adherence to chemotherapy (Vandergrift et al., 2013) and hormonal therapy (Partridge et al., 2003). Increasing age, low socioeconomic status, and health insurance are associated with longer time to chemotherapy (Vandergrift et al., 2013). Other factors cited in a study on non-adherence for chemotherapy by patients include forgetfulness, discontinuation of treatment, lack of information, and also emotional factors. While limited access to healthcare, complex administration schedules, high costs for drugs and co-payments are barriers by the healthcare system (Steve, 2008).

Major predictors of poor adherence to hormonal therapy have been well characterized. The treatment side effects is reported as the primary reason for non-adherence to hormone therapy (Kirk & Hudis, 2008). Besides, the likelihood of non-adherence to hormonal therapy are seen among young patients, alcohol drinkers, advanced cancer stage, those who received mastectomy and chemotherapy, and those who had more hospitalization (Brito et al., 2014; Partridge et al., 2003).

2.13 Impact of delays in breast cancer

2.13.1 Impact on progression of breast cancer

Delays in presentation, diagnosis and treatment of breast cancer may lead to progression of the disease. Many studies have been conducted to evaluate the impact of delays on stage and tumor size.

Previous studies amongst women with breast cancer in Malaysia found that those who delay presentation of more than 3 months had a significant association with advanced stage disease (Cheng et al., 2015; Ghazali et al., 2013; Mujar et al., 2013). Similar finding

is seen in other western studies. A systematic review has found that the delay presentation of more than 3 months would generally present with advanced stage (Richards et al., 1999). Recent studies reported that delay presentation is not only related to the advanced cancer stage but also associated with larger tumors size (Fujii et al., 2015; Montazeri et al., 2003). Therefore, longer duration of symptoms may be considered as an indicator of tumor progression.

In contrast, other studies found that delays do not appear to be significantly associated with more advanced stage breast cancer at diagnosis (Murchie et al., 2015). In addition, diagnostic delays of up to 36 months also do not correlate with worsening prognostic factors like tumor diameter, number of positive lymph nodes, tumor grade, or pathologic stage (Hardin et al., 2006).

2.13.2 Impact on survival

Many studies are conducted to evaluate whether delays from symptom discovery up to initial treatment in breast cancer impacts survival. The delays in breast cancer are generally thought to affect prognosis but the impact on survival remains unclear.

Studies revealed that survival is dependent on the cancer stage and is not associated with the time interval to treatment (Brazda et al., 2010; Hardin et al., 2006; Murchie et al., 2015). Another study reported that delayed presentation do not affect survival but prolonged consultation is associated with increased overall survival (Sainsbury et al., 1999).

In contrast to the above findings, a systematic review exploring the effect of delay presentation on survival has found that longer delays are associated with lower survival and those delayed for 3 months or more had 12% lower survival (Richards et al., 1999).

Similar findings are also seen in other studies (Bish et al., 2005; Facione & Facione, 2006).

2.14 Complementary and alternative medicine (CAM) use

Numerous studies had reported significantly high degree of CAM use in Malaysia. The prevalence of CAM use by breast cancer patients in Malaysia range from 25% to 88.3% (Chui et al., 2014; Knight et al., 2015; Raja et al., 2013; Saibul et al., 2012). High utilization of CAM is also found in other Asian countries such as 75.0% in Indonesia (Azhar & Achmad, 2015), 67% in Korea (Hwang et al., 2015), 60.9% in Thailand (Puataweepong et al., 2012), 55.0% in Singapore (Chow et al., 2010) and 47.3% in Turkey (Tas et al., 2016).

Studies shows among reasons for the reliance of CAM are patients were influenced by family members and friends, thought that CAM works, they previously had bad experience in hospital, financial problems, was afraid that she cannot work after the mastectomy, no time, having young children and was embarrassed to see doctors (Abdullah et al., 2013; Taib et al., 2007). Most patients took CAM as a way to avoid surgery and the perception that traditional medicine is more effective than modern medicine (Norsa'adah et al., 2011) and subsequently present late to hospital after they found that CAM was not effective (Norsa'adah et al., 2012; Taib et al., 2014). Although CAM use has been cited as a cause of delays in breast cancer in qualitative studies (Norsa'adah et al., 2012; Taib et al., 2011), there has not been any confirmatory study that confirms its impact on delays.

2.15 Conceptual framework

The reasons for delay in presentation, diagnosis and treatment of breast cancer are multi-factorial. Personal aspects, health systems, socio-cultural, psychological and accessibility to health care services plays an important role in determining the time taken to presentation, diagnosis and treatment of breast cancer. A comprehensive health service for breast cancer depends on the resources, facilities and specialties in every aspect. Figure 2.10 shows the relationships between factors that may cause delays in presentation, diagnosis and treatment of breast cancer in Malaysia. In this study, all the variables under the three main factors, except psychological and accessibility to health care services were collected and analysed.

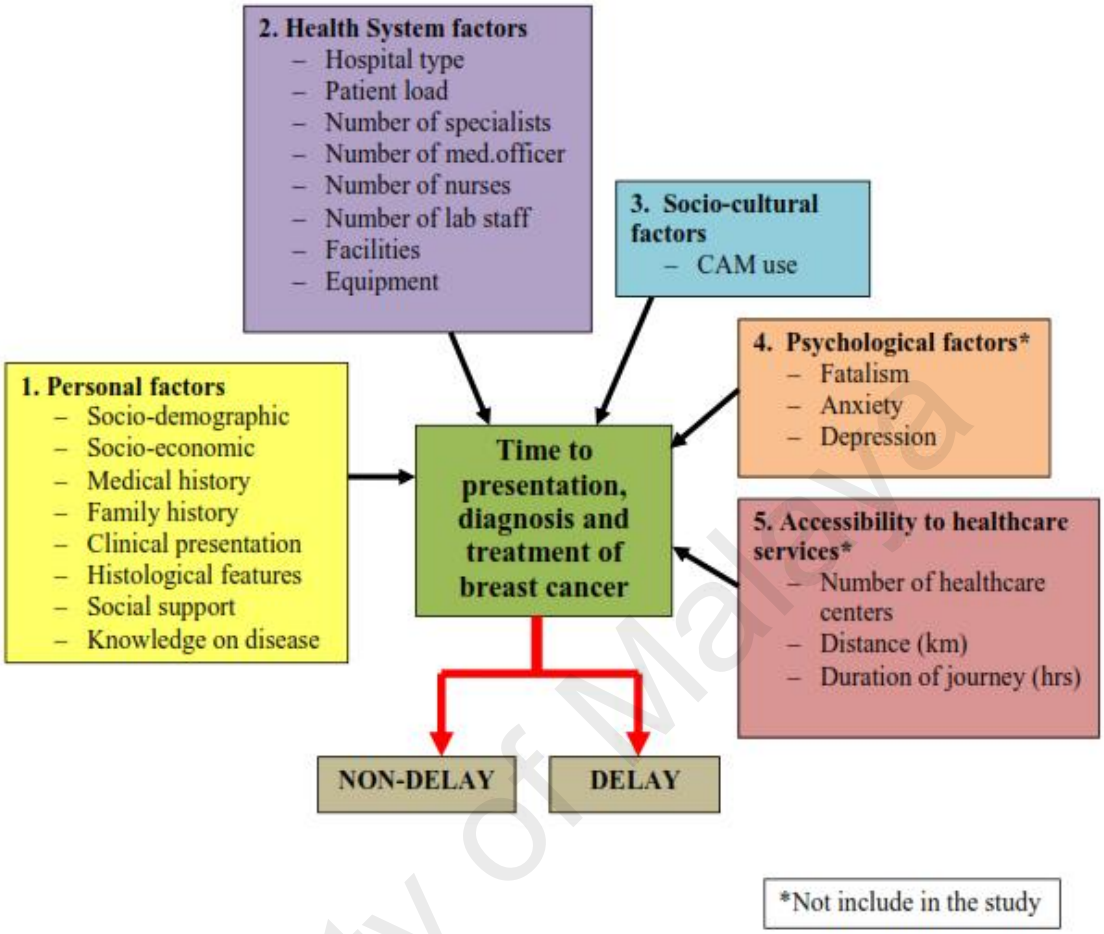


Figure 2.10: Conceptual framework

2.16 Chapter Summary

This chapter has discussed the significant issues in the study area and provided a comprehensive literature review. Delays in presentation, diagnosis and treatment, as well as non-adherence to cancer treatment were high among breast cancer patients and negatively impacted. Factors influencing delays and non-adherence were multifactorial including socio-culture, patients, health systems, psychological and accessibility to healthcare. Following that, a conceptual framework in explaining the topic of study was described extensively. The methods of the studies are discussed in detail in the next chapters.

CHAPTER 3: DELAY IN TIME TO PRIMARY TREATMENT AFTER A DIAGNOSIS OF BREAST CANCER AND IMPACT ON OVERALL SURVIVAL

3.1 Introduction

Delay in time to primary treatment could affect breast cancer prognosis (Richards et al., 1999) but the impact of delay on patients' survival is still unclear. Indicators for breast cancer care include time to primary treatment after a diagnosis. The purpose of this study is to evaluate the impact of the time interval between diagnosis and treatment initiation in breast cancer and overall survival.

Survival analysis was conducted to answer the first objective of the study (Objective no.1). This analysis was conducted prior to the main study using secondary data from University Malaya Medical Centre (UMMC). It was conducted to guide the construction of the questionnaires with special attention to variables available in clinical notes which are needed for main study.

3.2 Study objective

To evaluate the impact of time to primary treatment after a diagnosis of breast cancer and overall survival.

3.3 Literature Review

The optimal time to primary treatment of breast cancer cannot be defined and recommended to patients without evidence on the impact on outcomes. A systematic review exploring the effect of delays between the onset of symptoms and the start of treatment on survival has found that longer delays are associated with lower survival (Richards et al., 1999). Those delayed for 3 months or more had 12% lower survival

(Richards et al., 1999) and similar findings are also seen in other current studies (Bish et al., 2005; Facione & Facione, 2006; Smith et al., 2013).

In contrast to the above findings, previous and current studies in USA, UK, Turkey, Iran and Korea have found that no association between time to treatment after a diagnosis of breast cancer and survival (Brazda et al., 2010; Sainsbury et al., 1999; Samur et al., 2002; Shandiz et al., 2012; Yoo et al., 2016). It is believed that survival is dependent on the cancer stage and not associated with the time interval (Brazda et al., 2010; Hardin et al., 2006; Murchie et al., 2015). Even prolonged consultation is associated with increased overall survival (Sainsbury et al., 1999).

The impact of delay on breast cancer survival remains unclear. There has been scarcity of information in Malaysia on the acceptable duration of time intervals in breast cancer and whether this should be used as a quality indicator. Therefore, this study is done to evaluate whether time to primary treatment after a diagnosis of breast cancer impacts overall survival.

3.4 Methodology

3.4.1 Study design

This study is a nested cross-sectional study on retrospective cohort of breast cancer patients diagnosed at UMMC in year 2004 – 2005. The survival of patients according to their time from pathological diagnosis to primary treatment was determined.

3.4.2 Data source

Main data was obtained from UMMC Breast Cancer Registry (2004-2005). Survival statuses were obtained from National Registry of Birth and Deaths, medical records and information gathered from next of kin.

3.4.3 Study location

The location of the study was conducted in University Malaya Medical Centre (UMMC), Kuala Lumpur. UMMC is a teaching hospital and acted as a referral center for breast cancer cases. It has a comprehensive database known as UMMC Breast Cancer Registry and all patient information are collected prospectively since 1993.

3.4.4 Sampling frame

All 648 breast cancer patients who received treatment in University Malaya Medical Center (UMMC), between 1st January 2004 and 31st December 2005 were taken as study respondents.

3.4.5 Data information

Socio-demography, histopathology, medical history, presentation details, diagnosis details, treatment details and important dates (e.g. symptom duration, date of presentation, date of diagnosis, date of treatment, and date of death) were obtained from medical records. Survival status was obtained from the National Registry of Birth and Deaths, medical records and contacting next of kin.

3.4.6 Variables

3.4.6.1 Time to primary treatment (TPT)

Time to primary treatment (TPT) was defined as the time between the pathological diagnosis date to the date of primary treatment. Primary treatment was defined as the main or initial treatment which may be surgery or chemotherapy or hormonal therapy.

3.4.6.2 Overall survival

Overall survival was defined as number of months from the date of pathological diagnosis to the date of death or last follow-up. The last date of follow-up was December 2011.

3.4.5 Statistical analysis

Time to primary treatment (TPT) were analysed as a continuous variables (e.g. days, weeks, months) and were summarised as median (range (min-max)) due to non-normality distribution. Meanwhile, categorical variables were divided into a binary outcome; delay and non delay based on certain cut-off points (e.g. 2 weeks, 1 month, 2 months) and were summarised as frequency (percentage (%)).

Univariable logistic regression was conducted by using a 1 month cut-off point to ascertain factors associated with delay in time to primary treatment (TPT). One month was chosen instead of 2 months to allow balanced number of respondents in each category. Results were presented as the crude odd ratios (OR), 95% confidence interval (CI) and p value. The p value <0.05 was considered to indicate statistical significance. Significant variables were then entered into multivariable model by using multivariable logistic regression. A stepwise backward selection procedure was used. The interaction terms and multicollinearity problem of the final model were checked. The final model was tested for fitness using the Hosmer-Lemeshow goodness of fit test. Results were presented as adjusted odd ratios (OR), 95% confidence interval (CI) and p value. The p value <0.05 was considered to indicate statistical significance.

Survival analysis was conducted to determine the impact of time to primary treatment (TPT) upon overall survival of breast cancer patients. The TPT were analysed as a continuous variables (e.g. days, weeks, months) and categorical variables (e.g. 2 weeks, 1 month, 2 months). The overall survival was analysed by using Kaplan-Meier for univariate analysis. Results were presented as crude hazard ratios (HR), 95% confidence

interval (CI) and p value. The p value <0.05 was considered to indicate statistical significance.

Since time to primary treatment (TPT) had no impact on breast cancer survival, another univariate analysis was conducted to identify the interaction between significant factors and TPT upon overall survival. Kaplan-Meier analysis was used and results were presented as the crude hazard ratios (HR), 95% confidence interval (CI) and p value. The p value <0.05 was considered to indicate statistical significance. Multivariate analysis was not conducted because the interaction between TPT and stage at diagnosis upon overall survival was too low (crude HR 1.01 &1.02).

3.4.6 Ethics application

Ethics approval was obtained from the University Malaya Medical Centre (UMMC) (PPUM/MDU/300/04/03, 27th Oct 2011).

3.5 Results

3.5.1 Characteristic of breast cancer patients

A total of 648 patients were included in the study. The median age was 51 years (range 24 to 85 years) and majority of the respondents were Chinese (n= 422, 65.1%). A total of 504 (77.8%) patients were diagnosed at early stage cancer (stage 0, I, II) and 137 (21.1%) patients were diagnosed at late stage cancer (stage III, IV). Majority of the patients received surgery (88.3%) as their primary treatment followed by chemotherapy (8.8%) and hormonal therapy (2.9%).

Table 3.1: Characteristic of breast cancer patients

Characteristic		n (%)
Age group (years)	≤29	10 (1.5)
	30-49	275 (42.4)
	50-69	310 (47.8)
	>70	53 (8.2)
Ethnicity	Chinese	422 (65.1)
	Malay	147 (22.7)
	Indian	74 (11.4)
	Others	5 (0.8)
Stage	0	19 (2.9)
	I	167 (25.8)
	II	318 (49.1)
	III	83 (12.8)
	IV	54 (8.3)
	NA	7 (1)
Progesterone receptor	Negative	290 (44.7)
	Positive	309 (47.7)
	NA	49 (7.6)
Estrogen receptor	Negative	282 (43.5)
	Positive	333 (51.4)
	NA	33 (5.1)
Tumor size (cm)	≤2	632 (97.5)
	2.1-5.0	3 (0.5)
	NA	13 (2)
Type of treatment	Surgery	572 (88.3)

	Chemotherapy	57 (8.8)
	Hormonal therapy	19 (2.9)

3.5.2 Time to primary treatment after a diagnosis of breast cancer

The median time to primary treatment after a diagnosis of breast cancer was 18 days (1 day-15 months). The median time for surgery, chemotherapy and hormonal therapy were 18 days, 17 days and 13 days respectively. From the total number, 142 (21.9%) patients have delayed initial treatment of more than 1 month (30 days).

Table 3.2: Delay in primary treatment of breast cancer patients in UMMC, 2004-2005

Time interval	Cutoff points	N	Non-delay n (%)	Delay n (%)
Time to primary treatment	>1 month	648	506 (78.1)	142 (21.9)

3.5.3 Overall survival

The 5-year overall survival for patients with breast cancer in the University of Malaya Medical Centre was 77.9% (CI 76.89, 81.46).

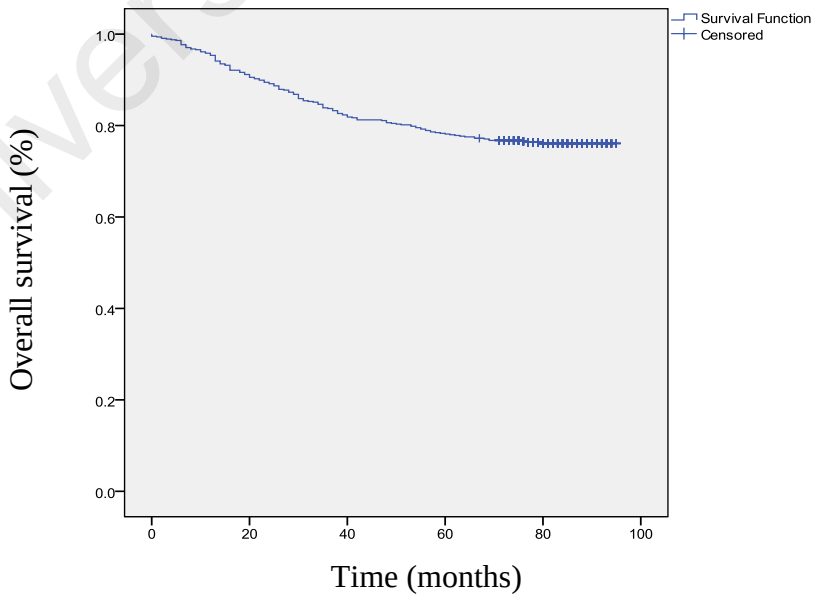


Figure 3.1: The 5-year overall survival

3.5.4 Factors associated with delay in time to primary treatment of breast cancer

Ethnicity and stage showed a significant association with delayed treatment in univariate analysis. However, after adjustment with other covariates in multivariate analysis, Malays (p=0.004) are significantly associated with delayed primary treatment OR: 1.92 (95% CI: 1.23, 2.98) compared to Chinese. This finding illustrates that Malay was 2 times more delay to primary treatment than Chinese.

Table 3.3: Factors associated with delay in time to primary treatment of breast cancer patients

Characteristic	**≤ 1month n=506 (78.1%)**	**> 1 month n= 142 (21.9%)**	**Univariate analysis**		**Multivariate analysis**	
			Crude OR (95% CI)	**P value**	**Adjusted OR (95% CI)**	**P value**
Ethnicity						
Chinese	346 (81.9)	76 (18.0)	1.00	-	1.00	-
Malay	100 (68.0)	47 (32.0)	1.52 (1.03, 1.91)	**0.002**	1.92 (1.23, 2.98)	**0.004**
Indian	55 (74.3)	19 (25.7)	0.147	0.160		
Others	5 (100)	0 (0)	1.21 (0.64, 2.68)	0.111	1.52 (0.84, 2.74)	0.999
			0.08 (0.00, 1.25)		0.00 (0.00, -)	
Age group, years					-	
≤29	6 (60.0)	4 (40.0)	1.00	-		
30-49	215 (78.2)	60 (21.8)	1.17 (0.13, 3.05)	0.195		
50-69	248 (80.0)	62 (20.0)	0.14 (0.06, 1.20)	0.258		
>70	37 (69.8)	16 (30.2)	0.82 (0.33, 2.71)	0.121		
Stage						
0	12 (63.2)	7 (36.8)	1.00	-	1.00	-
I	139 (83.2)	28 (16.7)	0.14 (0.10, 2.05)	0.178	0.37 (0.13, 1.05)	0.063
II	255 (80.2)	63 (19.8)	0.25 (0.16, 1.10)	0.221	0.45 (0.16, 1.20)	0.111
III	53 (63.9)	30 (36.1)	2.75 (2.33, 3.72)	**0.007**	0.95 (0.33, 2.71)	0.926
IV	42 (77.7)	12 (22.2)	1.22 (1.10, 1.32)	**0.042**	0.44 (0.14, 1.41)	0.171
NA	5 (71.4)	2 (28.6)	0.40 (0.08, 3.12)	0.231	0.60 (0.08, 4.04)	0.600

Tumor size, cm	491 (77.7)	141 (22.3)	1.00	-	-
≤2	3 (100)	0 (0)	0.84 (0.10,	0.296	
2.1-5.0	12 (92.3)	1 (7.7)	2.32)	0.364	
NA			1.42 (0.18,		
			1.90)		
Treatment					
Surgery	453 (79.2)	119 (20.8)	1.00	-	-
Chemotherapy	40 (70.2)	17 (29.8)	1.97 (0.44,	0.171	
Hormonal	13 (68.4)	6 (31.6)	3.15)	0.422	
therapy			2.16 (0.12,		
			4.01)		

Univariate analysis: Univariable logistic regression & Multivariate analysis: Multivariable logistic regression
OR: Odd Ratio, CI: Confidence Interval

3.5.5 Impact of delay in time to primary treatment of breast cancer on overall survival

Subsequently, Kaplan-Meier analysis was performed to evaluate the impact of time to primary treatment after a diagnosis of breast cancer upon survival. Delay in time to primary treatment in days, weeks and months did not affect survival. There was also no significant difference found in survival when using the cut-off points of 2 weeks, 1 month and 2 months. Therefore, time to primary treatment had no impact on breast cancer survival.

Since time to primary treatment (TPT) had no impact on breast cancer survival, another univariate analysis was performed to test the interaction of TPT with other covariates and their impact on survival. Ethnicity and stage at diagnosis were chosen because a significant relationship with delays. From the analysis, it was found that ethnicity did not have any association with TPT and survival. But, those who were diagnosed at stage 3 (HR=1.01, CI: 1.00, 1.08) and stage 4 (HR=1.02, CI: 1.01, 1.02) were the only factor that was associated with TPT and survival. Multivariate analysis was not conducted because the interaction between TPT and stage at diagnosis upon overall survival was low (crude HR 1.01 &1.02).

Table 3.4: Survival analysis on time to primary treatment of breast cancer patients

Time to primary treatment	N (%)	Crude HR (95% CI)	P value
Day	648 (100)	1.00 (0.99, 1.04)	0.874
Week	648 (100)	1.01 (0.98, 1.03)	0.625
Month	648 (100)	1.05 (0.95, 1.16)	0.305
TPT group			
≤2 weeks	281 (43.3)	1.00	-
>2 weeks	367 (56.6)	0.81 (0.59, 1.11)	0.191
TPT group			
≤1 month	506 (78.1)	1.00	-
>1 month	142 (21.9)	1.24 (0.86, 1.78)	0.250
TPT group			
≤2 month	602 (92.9)	1.00	-
>2 month	46 (7.1)	1.24 (0.70, 2.18)	0.465

Univariate analysis: Kaplan-Meier; TPT: Time to primary treatment,
HR: Hazard Ratio, CI: Confidence Interval

Table 3.5: Interaction between significant factors and time to primary treatment (TPT) upon survival of breast cancer patients

Interaction	N (%)	Crude HR[b]	P value[b]

		(95% CI)	
TPT*Ethnicity			
Chinese	422 (65.12)	1.000	-
Malay	147 (2.68)	1.00 (0.99, 1.01)	0.255
Indian	74 (11.42)	1.00 (0.99, 1.01)	0.951
Others	5 (0.77)	0.99 (0.89, 1.11)	0.919
TPT*Stage			
0, I, II	504 (77.78)	1.000	-
III	83 (12.8)	1.01 (1.00, 1.08)	**0.003**
IV	54 (8.3)	1.02 (1.01, 1.02)	<**0.001**
NA	7 (1.08)	0.99 (0.93, 1.05)	0.742

Univariate analysis: Kaplan-Meier, TPT: Time to primary treatment,
HR: Hazard Ratio, CI: Confidence Interval

3.6 Discussion

Our findings suggest a moderate time to primary treatment of within 18 days. This is similar to other studies in Malaysia during the period of breast cancer diagnosis to treatment of 19 days (Yip et al., 2011). Ethnicity was significantly associated with delaying treatment amongst the breast cancer patients as seen in other studies (Bustami et al., 2014; Caplan et al., 2000; Sasha et al., 2013), whereby noticeably patients of Malay ethnicity was found to be the independent factor for treatment delay. In a qualitative study, delay in treatment decisions by patients was the factor contributed towards treatment delay (Taib et al., 2014). Malays are thought to be dominated by a strong community relationship where family and friends involvement greatly influence the patients' treatment-seeking behavior (Muhamad et al., 2012) thus, indirectly led to delaying treatment. Furthermore, the high use of complementary and alternative medicine (CAM) among Malays compared than Chinese and Indian (Chui et al., 2014; Farooqui et al., 2015; Hamidah et al., 2009; Raja et al., 2013) may lead to this finding. Inattention to routine breast cancer screening, denial, and fatalism are the other factors for longer time to getting treatment as seen in other study (Mohamed et al., 2005).

Similar to recent studies in the breast cancer literature, our findings show that time to primary treatment has no impact on breast cancer survival. The time from diagnosis to primary treatment of greater than 2 weeks, 1 month and 2 months shows no effect on survival. This is supported by other studies where no association was found between time from diagnosis to treatment and breast cancer survival (Brazda et al., 2010; Sainsbury et al., 1999; Samur et al., 2002; Shandiz et al., 2012; Yoo et al., 2016). The impact on survival is more related to symptom duration rather than duration taken to treatment after a diagnosis. One previous study showed that patients with delay of 12 to 26 weeks had significantly worse survival rates with 12% lower 5-year survival (Richards et al., 1999). However, this study measured the time to treatment from the onset of symptom. Hence, quality indicators should include symptom duration and the time taken for diagnostic workup after presenting to hospital as these delays may impact survival rather than treatment time.

As seen in this study, time to primary treatment after diagnosis is not a good indicator for quality breast cancer care. The impact of treatment delays on survival may have been significant if time to primary treatment was calculated to include the duration of symptoms, but data on symptom duration was not recorded prospectively and many missing values thus, this date may well be inaccurate. Hence, we decided to use a more concrete date in this study which is the pathological diagnosis date.

Stage is a known prognostic factor in breast cancer survival. In this study, stage was found to have a significant interaction with delayed time to primary treatment. We believed that the health behavior of women who present late at stage III or IV may cause delay in making treatment decisions and impact their survival. Although primary systemic therapy is the treatment of choice in late staged disease and possibly the acceptable

waiting time for systemic treatment is generally longer than surgical waiting time, the median duration of chemotherapy and surgery is similar in this study.

Study suggests that survival is not related to the delay but with the stage at diagnosis. The hetereogenity of cancer biology cause some types of tumor are more aggressive than others, thus the effect on time may be mixed, hence the reason of why delay was not found to have any independent association to outcomes. Unfortunately, there is no predictive model to identify which patients who would be afflicted with the aggressive type of cancer. This emphasizes why patients should not delay, and early presentation, diagnosis, and adherence to treatment is generally accepted for optimum outcomes.

3.7 Limitation and strength of study

The limitation of this study is that the results may well be affected by the small sample size. When different cut-off points of 1 month and 2 months were used, the numbers in the delayed group were remarkably small. The findings are also limited to overall survival. The impact on disease free survival is not known due to unavailability of recurrence data. A larger prospective study with clearly defined time points from symptom discovery, diagnostic process until treatment completion is needed to measure the impact of delays on breast cancer survival. Also data on contribution of patient or system delays would be important to plan interventions. This would assist in drawing up meaningful quality indicators to breast cancer care and furthermore provides evidence to meaningful time points in counseling patients for treatment.

3.8 Contribution and Implications of the study

3.8.1 Modifiable prognostic factor

There was a significant interaction between the time to primary treatment with late stage at diagnosis and their impact on survival. This study suggests that survival is not related to the delay but with the stage at diagnosis. Therefore, stage at diagnosis is a modifiable prognostic factor and a strategy to reduce delay in presentation, diagnosis, and treatment may prove to be useful in order to improve survival.

3.9 Conclusion

Time to primary treatment after a diagnosis of breast cancer had no impact on overall survival in this study, hence may not be a meaningful breast cancer care quality indicator. Factors that affect delayed time to primary treatment were the patients' ethnicity and stage at diagnosis. Survival was not related to the treatment delay but with the stage at diagnosis which was a modifiable prognostic factor. Therefore, a strategy to reduce delay in presentation, diagnosis, and treatment may prove to be useful in order to improve survival. Clearly defined time points from symptom discovery, diagnostic process, and treatment initiation are needed to measure the impact of delays on breast cancer survival in the future.

3.10 Chapter summary

This chapter has been published in an article entitled "Delays in time to primary treatment after a diagnosis of breast cancer: Does it impact survival" (Mujar et al., 2013)

(Appendix A). The hetereogenity of cancer biology causes some types of tumor are more aggressive than others but no predictive model is available to identify which patients who would be afflicted with the aggressive type of cancer. Therefore, a strategy to reduce delay in presentation, diagnosis, and treatment may prove to be useful in order to improve survival, which is discussed in the next study.

CHAPTER 4: PRESENTATION, DIAGNOSIS AND ADHERENCE TO TREATMENT OF BREAST CANCER AMONGST PATIENTS ATTENDING PUBLIC HOSPITALS IN MALAYSIA: THE TIME INTERVALS AND ASSOCIATED FACTORS TO DELAY AND NON-ADHERENCE

4.1 Introduction

Delays in presentation, diagnosis, treatment and non-adherence to treatment could be the barriers for a better prognosis. Few studies focuses on the time interval of breast cancer patients, especially involving those attending public facilities in Malaysia. Moreover, at present there is no available national baseline data that would indicate periods of complete intervals from discovery of symptoms until the onset of treatment. Therefore, this study was conducted to investigate the time intervals involved in a complete breast cancer journey and associated factors to delays and non-adherence amongst breast cancer patients attending public hospitals in Malaysia.

The study's main issue generally responds to the other subsequent objectives as purported in the previous chapter, this is achieved by looking at both of the perspective from patient and health system. A multi-centre study nationwide composed of patients from diverse socio-demographic background and various locations of public hospitals should provide a better picture of breast cancer care, thus making it possible to infer to the whole of Malaysian population.

4.2 Study objective

1. To determine the time intervals between important time points in the breast cancer journey from symptom discovery to initial treatment.

2. To determine the proportion of delay in presentation, diagnosis and treatment of breast cancer patients.
3. To determine the factors associated with delay in presentation, diagnosis and treatment of breast cancer patients.
4. To determine factors associated with non-adherence to breast cancer treatments (e.g. surgery, oncology therapy) amongst breast cancer patients.

4.3 Literature Review

Breast cancer delay (BCD) was first introduced by Pack & Gallo (1938), and it refers to the elapsed time between the symptoms discovery and the initiation of medical treatment. It is divided into two categories which are 'patient delay' and 'system delay'. Patient delay is caused by the patient in seeking medical attention after self-discovering a potential breast cancer symptom (Caplan, 2014), while system delay is caused by the health care system and/or patients in getting appointments, scheduling diagnostic tests, receiving a definitive diagnosis, and initiating therapy (Caplan, 2014; Taib et al., 2014).

The three intervals of delays; presentation, diagnosis and treatment were used in this study as it is more accurate in a quantitative study. However, there is no standardized measurement for these three delays as each researcher used different measurement points. Based on previous studies, 3 months (Cheng et al., 2015; Ghazali et al., 2013; Memon et al., 2013; Mody et al., 2013; Pakseresht et al., 2014b; Poum et al., 2014; Ruddy et al., 2014), 30 days (Ermiah et al., 2012; Huo et al., 2014; Plotogea et al., 2014; Shieh et al., 2014) and 30 days (Caplan et al., 2000; Jung et al., 2011; Molinié et al., 2013; Pérez et al., 2008; Rastad et al., 2012; Shandiz et al., 2012) have commonly been used as cut-off points for presentation delay, diagnosis delay and treatment delay respectively and thus, which were used in this study.

Delay in presentation is common among breast cancer patients in Malaysia (Taib et al., 2007) with 33-59% had delayed presentation by more than 3 months (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011). High prevalence of 17-60% presentation delay is also found in other Asian countries (Harirchi et al., 2005; Khan et al., 2015; Memon et al., 2013; Montazeri et al., 2003; Pakseresht et al., 2014a; Poum et al., 2014; Yau et al., 2010) and much higher of 80-85% in African countries (Galukande, 2014; Ibrahim & Oludara, 2012; Mody et al., 2013). In contrast, lower prevalence of presentation delay can be seen in western countries with 19% in London (Burgess et al. 1998) and 17% in United States (Ruddy et al., 2014). Despite high incidence of breast cancer, women in western countries typically presented early due to increased public awareness of symptom appraisal and more openness about breast cancer (Bairati et al., 2007). In combination with population based screening programs for earlier detection and efficient treatments by mature high resource health care systems, survival rates for breast cancer has improved over recent years (Globocan, 2013; Schwentner et al., 2013).

A study on diagnosis delay conducted in Malaysia found that 72.6% and 45.5% delayed more than 3 months and 6 months respectively after detecting symptoms in the east coast of the Malaysian peninsular (Norsa'adah et al., 2011). However, no study was performed in Malaysia to assess the actual diagnostic interval from the first presentation at primary care until a diagnosis resolution. Longer referral time is partially responsible for the diagnosis delay which attributed by the decision-making process by both the patients and health system (Jassem et al., 2013; Taib et al., 2014). Patient might not attend to the diagnostic center when they decided to ignore the symptoms (Taib et al., 2014; Yu et al., 2015), has negative beliefs of cancer (Norsa'adah et al., 2012) or too much reliance on family decision (Macleod et al., 2009; Mccain et al., 2011; Pace et al., 2015). Meanwhile, poor communication between patients and doctors, failure to recognize cancer symptom, not knowing where to refer the patient and additional hospital visits are

the barriers for prompt reference by the system (Taib et al., 2014; Taib et al., 2011; Pace et al., 2015). Efforts to reduce diagnosis delay concentrating on referral time within 2 weeks (Ireland National Cancer Registry, 2012; Mccain et al., 2011) and 4 weeks after presentation (Burgess et al., 1998; Jones et al., 2014) have been emphasized in the UK and US. However, there is no consensus or standardized timeframes for referral that has been applied in Malaysia and other Asian countries.

Delay in time to primary treatment of breast cancer conducted in a university hospital in Kuala Lumpur found that 21.9% delayed treatment of more than 1 month (Mujar et al., 2013), which is better than 52% in Hong Kong (Yau et al., 2010). This finding could be attributed by the type of health care facility as seen a study in US reported that the interval to treatment of breast cancer is shorter at a university hospital than a general hospital (Brazda et al., 2010). Therefore, there is a need to assess the time intervals at public general hospitals providing diagnostic and treatment to the majority of the Malaysian population. In addition, those who had an MRI, refused treatment, sought care in another centre and used alternative or traditional treatment are the significant factors of longer treatment interval seen in other studies (Chui et al., 2014; Chui et al., 2015; Hulvat et al., 2010; Leong et al., 2007; Lim et al., 2014).

Since delay is related to poor prognosis, it is important to minimize delays in presentation, diagnosis, and treatment of breast cancer. Timely access to health care services has become a priority in public health policies in western countries (Burgess et al., 1998; Caplan et al., 2000; Landercasper et al., 2010). Efforts to reduce delay have been emphasized in practice guidelines (Ermiah et al., 2012). Although the Clinical Practice Guidelines (CPG) for breast cancer in Malaysia has recommended the duration of two months interval from presentation to initial treatment (Ministry of Health Malaysia, 2010), no studies or audits have been done to assess these guidelines.

This study is primarily concerned with newly diagnosed breast cancer and the time evaluation. Hence, the main objective of this study is to explore the time interval of presentation, diagnosis and treatment, and non-adherence to breast cancer treatments. The other objective is to determine the associated factors to delays and non-adherence amongst newly diagnosed breast cancer patients attending public hospitals in Malaysia. Information from this study will assist clinicians and policy makers to formulate within hospital strategies and implement public health activities that can prevent delays in presentation, diagnosis and treatment as well as improve adherence to treatment of breast cancer in the future.

4.4 Methodology

4.4.1 Study approach

This study uses the approach of a quantitative method by using an interviewer guided questionnaires. Strategy of inquiry used in this study is an observational analytic study. It is considered natural experiment because the exposure occurs in a natural setting without any elements (i.e. intervention or treatment) during the study process. Observational research provides a quantitative or a numeric description of trends, attitudes, or opinions of a population by studying a sample of that population. (Aschengrau & Seage, 2003). The design can test specific aetiologic hypotheses which later may suggest a mechanism of causation (Friis & Sellers, 2009).

4.4.2 Study Design

This study is a retrospective cohort study, a longitudinal study that involves the analysis of data collected from a population or a representative subset at long latent period of time (Bland, 2001). Retrospective cohort study is a study design where one or more samples are followed retrospectively and subsequent status evaluations with respect to a

disease or outcome are conducted to determine which initial participants exposure characteristics are associated with it. This study design was selected because it is the most appropriate design, used to investigate the causes of disease or outcome, between the risk factors and delays. It is useful for public health planning to understand the disease. Cohort study has the advantage to examine a range of disease or outcomes caused by one exposure and very suitable for disease with a long latent period such as cancer. The noticeable limitation is this study design is not suitable for rare diseases, and has to follow a large number of subjects for a long period of time which can be very expensive and time consuming (Pine et al., 1997).

In this study, all breast cancer patients who diagnosed at 6 public hospitals in year 2012 were selected. Patients were observed and followed retrospectively to look at the time intervals along the breast cancer journey from discovering of breast cancer symptoms until receiving and completing treatments. The time intervals and associated factors to delays were determined.

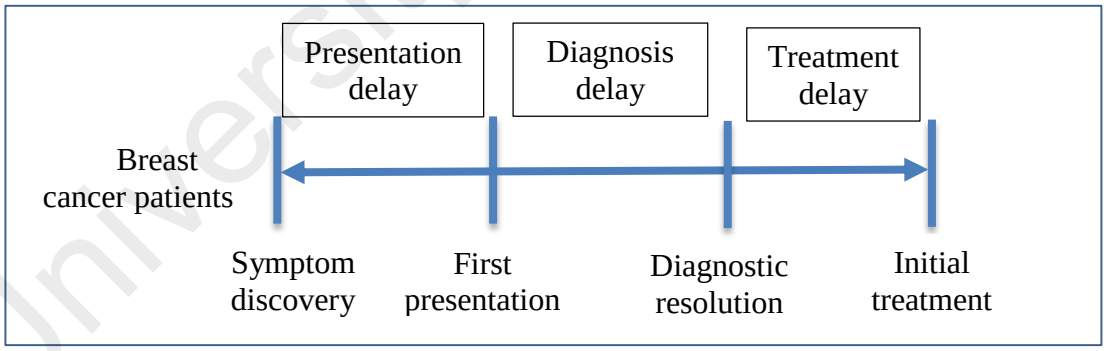


Figure 4.1: The time flow of the study

4.4.3 Study population

The study population consisted of newly diagnosed breast cancer patients attending public hospitals in Malaysia.

4.4.4 Sampling frame

The sampling frame consists of breast cancer patients diagnosed by histo-pathological examination (HPE) between 1st January and 31st December 2012. The list of those patients was obtained from the hospital registry and the breast cancer records at the Surgery Out-Patient Department (SOPD) or Breast Clinic in each hospital.

4.4.5 Sampling method

The sampling method was based on universal sampling design which refers to the selection of all people from the targeted population or whatever individuals happen to be easiest to access as participants in a study. It is a non-probability sampling whereby not all people in the population have the same chance of being included and the likelihood of being selected of each one of them is unknown. Universal sampling was conducted because it is the best choice of sampling techniques for this study. Therefore, a good representation of the overall population is possible in comparison with other type of sampling method. In this study, all newly diagnosed breast cancer patients at 6 participating public hospitals were recruited.

4.4.6 Study period

All breast cancer patients recruited in the study were followed up with a median of 14 months (range: 12 to 18 months) from diagnosis.

4.4.7 Study locations

This study took place in five (5) cities, which situated in Kuala Lumpur, Ipoh, Johor Bahru, Kota Bharu and Kuching. In the College of Surgeons meeting in 2012, breast surgeons and general surgeons in tertiary public hospitals were invited to participate but only six (6) public hospitals participated. The hospitals were University Malaya Medical Center (UMMC), Hospital Kuala Lumpur (HKL), Hospital Raja Permaisuri Bainun (HRPB), Hospital Sultan Ismail (HSI), Hospital Raja Perempuan Zainab (HRPZ) and

Hospital Umum Sarawak (HUS). List of the participating public hospitals is shown in Table 4.1.

Malaysia has five regions, namely Central, Northern, Southern, Eastern and East-Malaysia. Kuala Lumpur is situated in the Central region, Ipoh is situated in the Northern region, Johor Bahru is situated in the Southern region, Kota Bharu is situated in the Eastern region while Kuching is situated in the East-Malaysia region. Based on these study locations, sampling were taken from the entire regions in Malaysia.

The six public hospitals are the main hospital in each area and act as a referral centre for the breast cancer patients. Public hospitals in this study are defined as tertiary public health care facilities. These hospitals are owned by the government or semi-government and receive either fully or partial government funding. They are governed either under the Ministry of Health or the Ministry of Higher Education, Malaysia.

Public hospitals have been chosen in this study to obtain a baseline data on the time intervals of breast cancer journey in public hospitals in Malaysia. Findings of the Malaysia Health Expenditure Report in 2012, shows that the public health spending was higher than the private sector (MOH, 2014). This suggests that the utilisation of medical care in public hospitals was higher by the Malaysian population compared to the private hospitals. Moreover, the Healthcare Performance Measurement & Reporting System (HPMRS) (Yip et al., 2011) has covered breast cancer services in the private sector, thus this study aim to understand the situation in the public sector.

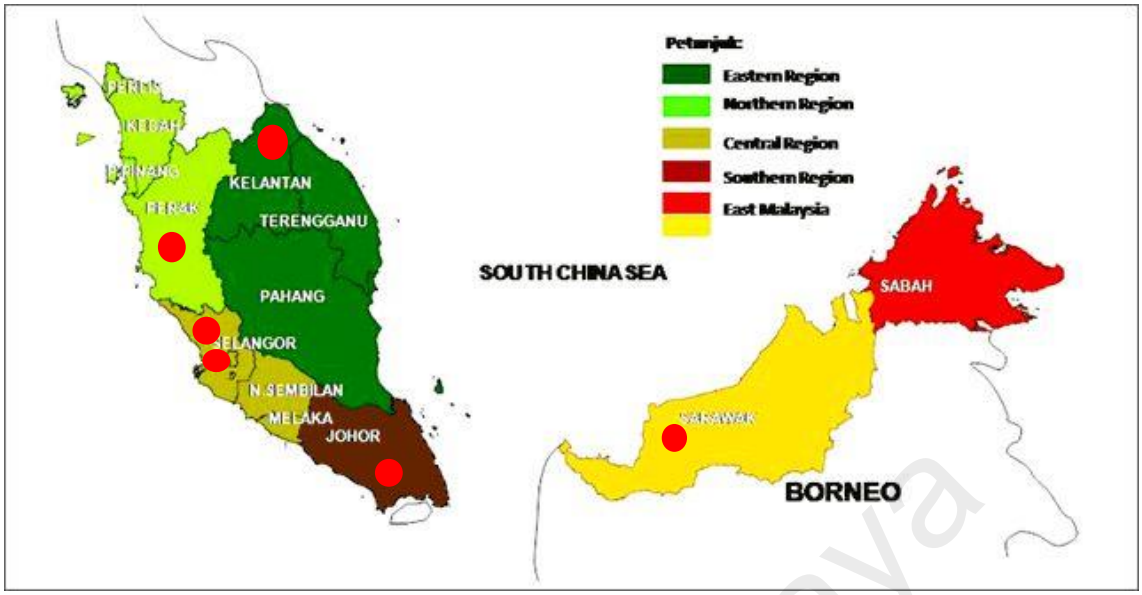


Figure 4.2: The location of six participating public hospitals

Table 4.1: List of the participating public hospitals

Public Hospitals	City	Region
1. University Malaya Medical Center (UMMC)	Kuala Lumpur	Central
2. Hospital Kuala Lumpur (HKL)	Kuala Lumpur	Central
3. Hospital Raja Permaisuri Bainun (HRPB)	Ipoh, Perak	Northern
4. Hospital Sultan Ismail (HIS)	Johor Bahru, Johor	Southern
5. Hospital Raja Perempuan Zainab (HRPZ)	Kota Bharu, Kelantan	Eastern
6. Hospital Umum Sarawak (HUS)	Kuching, Sarawak	East-Malaysia

4.4.8 Details of the six (6) participating public hospitals

4.4.8.1 University Malaya Medical Centre (UMMC)

UMMC is situated in an urban area in the central region of Malaysia. This hospital caters to the low, middle and high income patients and serve as a teaching hospital with 957 beds. Approximately, there are 7,000 breast clinic patient visits per year and 325 patients were diagnosed with breast cancer in 2012. There are 4 breast surgeons, 23 general surgeons, 9 oncologists, 6 pathologist, 50 medical officers and 27 housemen. The surgery department is supported with 154 nurses, 13 attendants and assisting staff and 10 lab personnel. Multidisciplinary care is offered at this hospital such as screening, diagnostic services, surgery and treatments. Facilities and equipment like mammography, ultrasound, x-rays, CT scan, bone scan and MRI are available. A whole range of breast cancer surgery including sentinel node biopsy and breast reconstruction as well as oncology treatments like chemotherapy, radiotherapy, hormonal and targeted therapy are also offered in UMMC.

4.4.8.2 Hospital Kuala Lumpur (HKL)

HKL is situated in an urban area in the central region of Malaysia. This hospital caters to the low and middle income patients and serve as a general state hospital with 2,229 beds. Approximately, there are 7,000 breast clinic patient visits per year and 230 patients were diagnosed with breast cancer in 2012. There are 3 breast surgeons, 2 general surgeons, 8 oncologists, 8 pathologist, 30 medical officers and 100 housemen. The surgery department is supported with 156 nurses, 59 attendants and assisting staff and 18 lab personnel. Multidisciplinary care is offered at this hospital such as screening, diagnostic services, surgery and treatments. Facilities and equipment like mammography, ultrasound, x-rays, CT scan, bone scan and MRI are available. Whole range of breast cancer surgery including sentinel node biopsy and breast reconstruction as well as

oncology treatments like chemotherapy, radiotherapy and hormonal therapy are also offered in HKL.

4.4.8.3 Hospital Raja Permaisuri Bainun, Ipoh (HRPB)

HRPB is situated in an urban area in the northern region of Malaysia. This hospital serves as a state referral hospital with 990 beds. Approximately, there are 300 breast clinic patient visits per year and 80 patients were diagnosed with breast cancer in 2012. There are 1 breast surgeon, 3 general surgeons, 15 medical officers and 30 housemen. There is no oncologist in HRPB. All chemotherapy and radiotherapy cases are referred to Hospital Kuala Lumpur (HKL) or Hospital Pulau Pinang (HPP). However, chemotherapy is given by the surgical department in HRPB. The surgery department is supported with 50 nurses, 10 attendants and assisting staff and 7 lab personnel. The hospital mainly provides screening, diagnostic and surgical treatments. Facilities and equipment like mammography, ultrasound, x-rays and CT scan are available. Surgery and hormonal therapy were offered in HRPB but not sentinel node biopsy, breast reconstruction, chemotherapy and radiotherapy.

4.4.8.4 Hospital Sultan Ismail, Johor Bahru (HSI)

HSI is situated in an urban area in the southern region of Malaysia. This hospital serves as a state referral hospital with 704 beds. Approximately, there are 250 breast clinic patient visits per year and 68 patients were diagnosed with breast cancer in 2012. There are 2 breast surgeons, 3 general surgeons, 4 oncologists, 12 medical officers and 27 housemen. The surgery department is supported with 35 nurses and 5 attendants and assisting staff. Pathological services are out-sourced to Hospital Sultanah Aminah, Johor Bahru (HSAJB). Facilities and equipment like mammography, ultrasound, x-rays and CT scan are available. Surgery, chemotherapy and hormonal therapy are also offered for treatments in HSI, but not sentinel node biopsy, breast reconstruction and radiotherapy.

4.4.8.5 Hospital Raja Perempuan Zainab II, Kota Bharu (HRPZII)

HRPZ is situated in an urban area in the eastern region of Malaysia. This hospital serves as a referral state hospital with 920 beds. Approximately, there are 400 breast clinic patient visits per year and 67 patients were diagnosed with breast cancer in 2012. There are 2 breast surgeons, 5 general surgeons, 3 pathologist, 20 medical officers and 25 housemen. There is no oncologist in HRPZ. All chemotherapy and radiotherapy cases are referred to Hospital Universiti Sains Malaysia (HUSM). However, chemotherapy is given by the surgical department in HRPZ. The surgery department is supported with 100 nurses, 20 attendants and assisting workers and 5 lab staffs. Facilities and equipment like mammography, ultrasound, x-rays and CT scan are available. Bone scan was referred to HUSM. Surgery, breast reconstruction and hormonal therapy are offered in HRPZ but not sentinel node biopsy, chemotherapy and radiotherapy.

4.4.8.6 Hospital Umum Sarawak, Kuching (HUS)

HUS is situated in an urban area of East-Malaysia region. This hospital serves as a referral state hospital with 765 beds. Approximately, there were 300 breast cases and 100 patients were diagnosed with breast cancer in 2012. There are no breast surgeons, but they have 7 general surgeons, 3 oncologists, 2 pathologist, 14 medical officers and 40 housemen. The surgery department is supported with 48 nurses, 8 attendants and assisting staff and 5 lab staffs. Facilities and equipment as mammography, ultrasound, x-rays, CT scan are available. Surgery, chemotherapy, radiotherapy and hormonal therapy are offered in HUS, but not sentinel node biopsy and breast reconstruction.

Table 4.2: Characteristics of the public hospitals based on facilities and services offered

Participating hospitals	UMMC	HKL	HRPB	HSI	HRPZII	HUS

Regions	Center	Center	Northern	Southern	Eastern	East Malaysia
Hospital type	university hospital	state hospital	state hospital	regional hospital	state hospital	state hospital
Number of bed	957	2229	990	704	920	765
Patient load (2012):						
1. Breast cancer cases	325	230	80	68	67	100
2. Breast cases	7000+	7000+	300+	200+	300+	300+
Number of specialist:						
1. Breast surgeon	4	3	0	2	2	0
2. General surgeon	23	2	3	3	5	7
3. Oncologist	9	8	0	4	0	3
4. Pathologist	6	8	3	2	3	2
Number of medical staff:						
1. MO	50	30	15	12	20	14
2. Houseman	27	100	30	27	25	40
Number support staff:						
1. Nurses	154	156	50	35	200	48
2. Attendant	13	59	10	5	20	8
3. Lab staff	10	18	7	HSA	5	5
Facilities & equipment:						
1. MMG	√	√	√	√	√	√
2. Ultrasound	√	√	√	√	√	√
3. X-rays	√	√	√	√	√	√
4. CT Scan	√	√	√	√	√	√
5. Bone scan	√	√	N/A	N/A	HUSM	N/A
6.. MRI breast	√	√	N/A	N/A	N/A	N/A
Treatment available:						
1. Surgery	√	√	√	√	√	√
2. Chemo	√	√	HKL	√	HUSM	√
3. Radiotherapy	√	√	HKL	HSA	HUSM	√
4. Others	Recon. surgery	Recon. surgery	N/A	N/A	Recon. surgery	N/A

*√ = available, N/A= not available, MMG= mammogram, Recon. surgery= reconstructive surgery,
HKL: Hospital Kuala Lumpur, HSA= Hospital Sultanah Aminah, HUSM= Hospital Universiti Sains Malaysia

4.4.9 Study criteria

The purpose of the inclusion and exclusion criteria is to establish precision in the study. It increases the likelihood of reliable and reproducible study outcome.

Inclusion and exclusion criteria applied in this study are listed as below:

Inclusion	• Newly diagnosed breast cancer patients • Attended and registered at the six public hospitals • Diagnosed by histopathology examination between 1st January and 31st December 2012 • Available medical records • Consented to be a respondent
Exclusion	• Recurrent breast cancer • Diagnosed with other cancers • Male breast cancer

4.4.10 Ethics application

Honesty and integrity were maintained while conducting this study. To ensure that the study was ethical, the rights to self-determination, anonymity, confidentiality and informed consent were assured so that the rights of the patients were protected.

Ethical approvals for this study was obtained from University Malaya Medical Centre (UMMC) Ethic Committee (PPUM/MDU/300/04/03) and was registered with the National Medical Research Register (NMRR), the Ministry of Health, Malaysia ((2)dlm.KKM/NIHSEC/08/0804/P12-824). Written permission was also obtained from the Hospital Directors, Head of Hospital Research and Ethical Committees and Head of Medical Record Unit of all six (6) public hospitals. Patient consent was obtained prior to data collection.

4.4.11 Study procedure

The search strategy begins in January 2012 after obtaining ethical approval from the University Malaya Medical Center Ethics Committee (UMMC) and the National Medical Research Register (NMRR). Study procedures were initiated with obtaining written consent from each of hospital director. Next, a meeting was conducted starting at

University Malaya Medical Center, Hospital Kuala Lumpur, Hospital Raja Permaisuri Bainun, Hospital Sultan Ismail, Hospital Raja Perempuan Zainab and Hospital Umum Sarawak. An approval was obtained from the breast surgeon or general surgeon in each hospital to obtain the list of newly diagnosed breast cancer patients. The study approvals and logistics matters for all hospitals have taken one year of period.

Data collections have started in January 2013. In the recruitment of respondents, every breast cancer patient who had attended the surgical out-patient department (SOPD) or breast clinic in each hospital was identified through the hospital registry and record book. The list of patients consisted of those who were diagnosed, treated and referred to the participating public hospitals. The information retrieved from the hospital registry and record book was full name, identification card number, registration number and date of diagnosis (1st January to 31st December 2012). Full name, identification card number and registration number were important for obtaining patients medical records from the record department while date of diagnosis was important for confirming newly diagnosed breast cancer patients.

The list of patients was then given to the records department in each hospital to be traced. The list of patients was divided according to the months of diagnosis and was consecutively requested according to the month of diagnosis which started in January 2012 and continued until December 2012. An effort has been made to acquire all the medical records. However, in situations where the medical records were not available after three requests were made, the patients were removed from the study. Each available medical record was then examined according to the inclusion and exclusion criteria. Only those that fulfilled the eligibility criteria were taken into the study.

Data collection was conducted by using a self-devised questionnaire known as "Breast Cancer Delay Survey" (Appendix D). After getting information from the medical

records, all eligible patients were then contacted through phone calls by the researcher to obtain consent to participate in the survey. To procure a high response rate, we avoided contacting the patients during peak hours. The patients were then briefly informed regarding the study objectives and subsequently invited to participate. Patients were encouraged to ask the researcher for any clarification and consent was taken prior to data collection. All eligible patients who agreed to participate were then scheduled for an interview. An appointment was scheduled after discussion based on the patients' preferred date and time. However, due to ethical consideration those who refused to participate were excluded from the study. All data collection was ended in June 2014.

Data entry and cleaning was done in preparation for data analysis, leadings to the exclusion of some patients diagnosed with recurrent cancer and incomplete dates as this study was primarily concerned with newly diagnosed breast cancer patients and time evaluation. All data entry and cleaning were ended in June 2015. Flow chart of study procedure is shown in Figure 4.3.

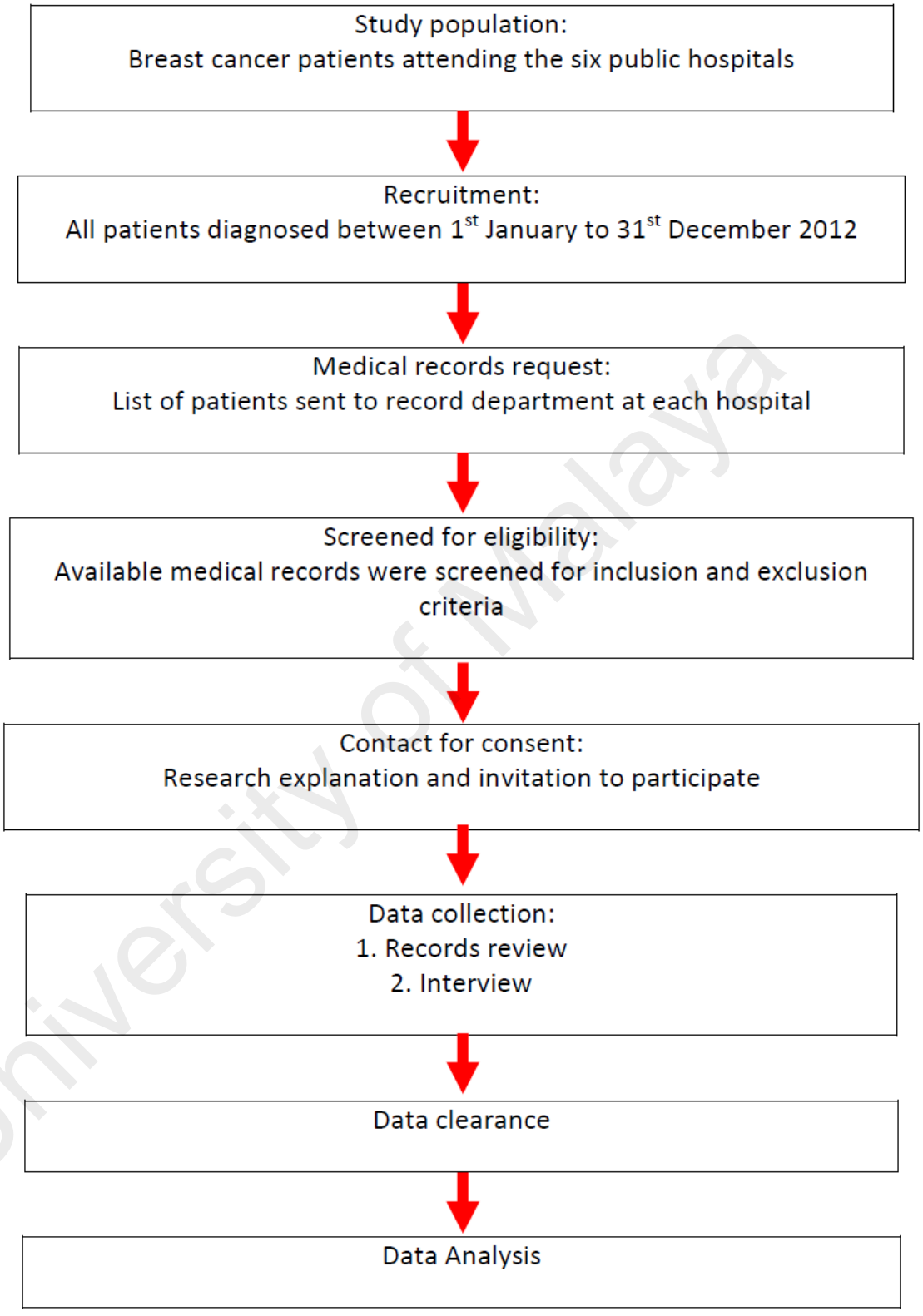


Figure 4.3: Flow chart of study procedure

4.4.12 Data collection

The data collection was conducted by the researcher with the help of one enumerator at each site. They possessed adequate clinical background and specifically trained for this study. Data collection was conducted through medical record review and interview. The reliance to only use medical records or database registry limit the quality of information and so only the available data can be used. Besides, the delay has been shown to be underestimated when calculated based on information obtained from medical records alone (Unger-Saldaña & Infante-Castañeda, 2009). Therefore, additional interviews were conducted to complete the data collection and ensure validity and accuracy of the data.

4.4.12.1 Medical records review

During the medical records review, patient's medical records and other related documents such as referral letters, medical notes, diagnostic forms, pathology reports and treatment records (i.e. surgery, chemotherapy, radiotherapy and hormonal therapy) were reviewed. The data obtained through the records review were details on each and every matter related to breast symptoms, presentation, diagnostic, histopathology and treatments of breast cancer, and date of all time points (e.g. symptom duration, date of primary care visit, date of referral, date of diagnostic centre visit, date of first biopsy, date of pathology reports, date of diagnostic resolution, date of start treatment, date of complete treatment).

4.4.12.2 Interview

The data on socio-demographic, medical and obstetric history, family history of breast cancer, practice of breast self-examination (BSE), adherence to hormonal therapy, uses of complementary and alternative medicine (CAM) and all missing information from record review were obtained from the interview. Adherence to hormonal therapy was based on 1-year after diagnosis. The interview was conducted either in person or via

telephone call based on the patients' preference. This was necessary to attract patients to voluntarily participate and increase response rate.

The interview sessions were conducted in an appropriate and convenient location to ensure patients are comfortable to answer the questions. Person to person interview was conducted at the hospital while the telephone interview was conducted while patient was at her house. The interview session takes about 30-45 minutes and questionnaire was completed at the time of interview. The interview was also conducted by proxy, through relatives if the patients were unable to communicate in either Malay or English.

An agreement was made after a discussion with the patients if there were conflicting or missing values. The patients were reminded of the previous date or events (e.g. birthday, national day, festivals session) in the calendar year to help them remember important dates or events relating to their medical history. Comparisons were done between both sources, records review and interviews to increase the data validity and accuracy.

4.4.13 Conceptual and operational definitions

4.4.13.1 Breast cancer delay

The terminology is referred to the time taken from symptom discovery to beginning of initial treatment (Pack & Gallo, 1938; Richards et al., 1999; Bish et al., 2005; Harirchi et al., 2005).

4.4.13.2 Newly diagnosed breast cancer

All new cases diagnosed with breast cancer by histopathology examination (HPE) regardless of the place of diagnosis. If cases have been referred from other healthcare facilities, details of diagnosis will be traced from referral letter or medical records.

4.4.13.3 The time intervals of the breast cancer journey

The time intervals of the breast cancer journey were divided into 3 groups; presentation interval, diagnosis interval and treatment interval. These time intervals were then divided into a binary outcome; delay and non-delay, by using cutoff points from literature review. The time intervals between important time points in the breast cancer journey are shown in Figure 4.4.

4.4.13.4 Presentation interval

The interval was defined as the time taken from the first symptom discovery to the first presentation at a primary care facility. Presentation delay is defined if it is more than 3 months duration (Lim et al., 2015; Facione & Facione, 2006; Ghazali et al., 2013; Harirchi et al., 2005; Norsa'adah et al., 2011; Unger-Saldaña & Infante-Castañeda, 2009; Montazeri et al., 2003).

4.4.13.5 Diagnosis interval

The interval was defined as the time taken from first presentation at a primary care facility to a diagnostic resolution. Diagnosis delay is defined if it is more than 1 month (30 days) duration (Bairati et al., 2007; Ermiah et al., 2012; Huo et al., 2014; Plotogea et al., 2014; Pruitt et al., 2014; Samphao et al., 2009).

Diagnosis interval was thoroughly divided into another 4 time intervals:

1. Referral interval: The time taken from referral to the diagnostic centre.
2. Biopsy interval: The time taken to do biopsy.
3. Report interval: The time taken to get histological report of confirmed malignancy.
4. Disclosure interval: The time taken to disclose diagnosis.

4.4.13.6 Treatment interval

The interval was defined as the time taken from the diagnostic resolution to initiation of treatment. Treatment delay is defined if it is more than 1 month (30 days) duration (Caplan et al., 2000; Pack & Gallo, 1938; Pérez et al., 2008; Rastad et al., 2012; Sainsbury et al., 1999; Shandiz et al., 2012).

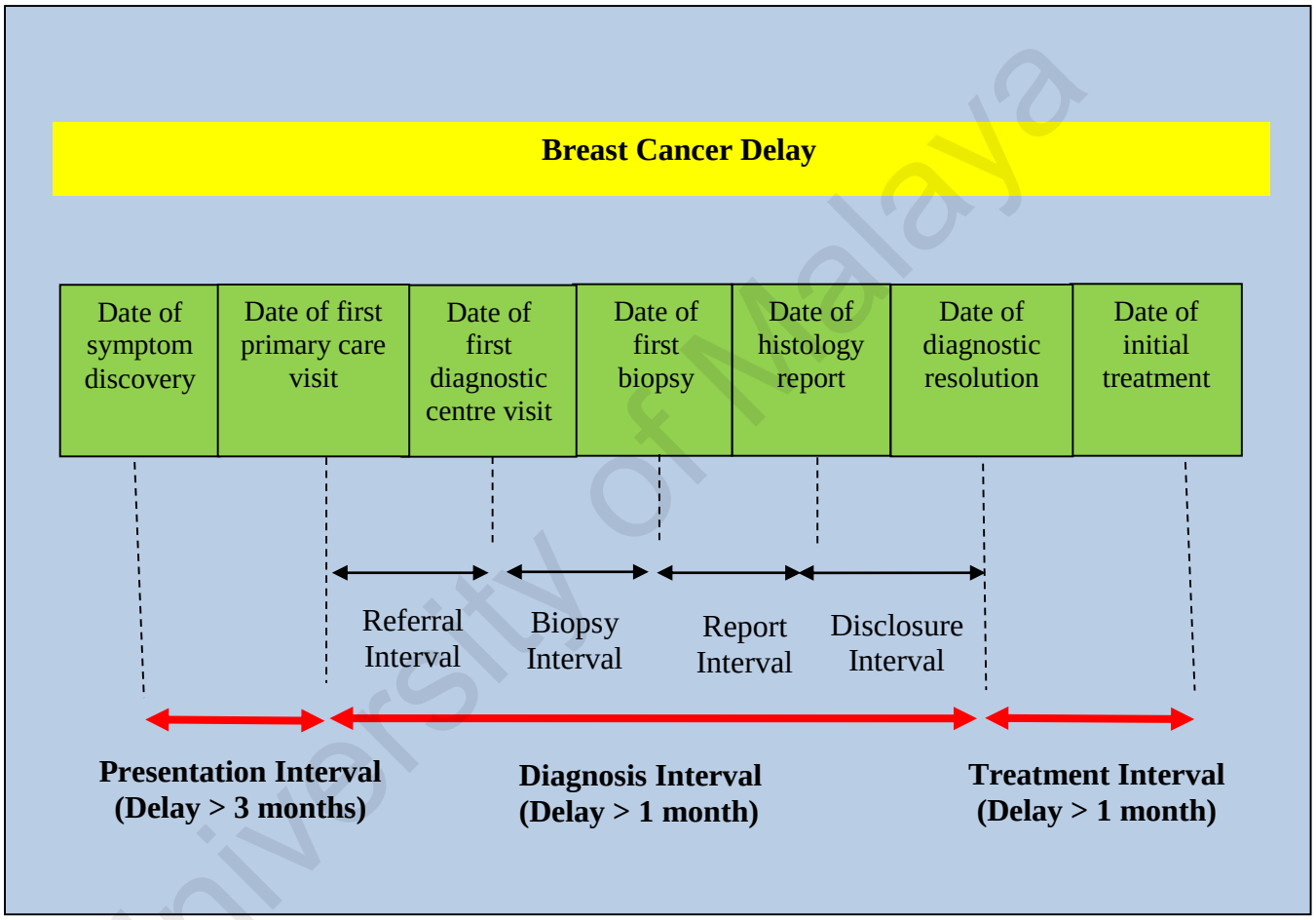


Figure 4.4: Time intervals between important time points in the breast cancer journey

4.4.14 Definition of dates of all time points

Dates of all time points were extracted from the patients' medical record and supported with interviews.

4.4.14.1 Symptom duration

Refers to the duration of symptoms before presenting to a primary care facility.

4.4.14.2 Date of first presentation

Refers to the date of the first presentation to a primary care facility (e.g. private clinic, public clinic, accident and emergency (A&E), out-patients department (OPD)).

4.4.14.3 Date of first diagnostic centre visit

Refers to the date of the first visit at the diagnostic centre (e.g. surgical out-patient department (SOPD), breast clinic).

4.4.14.4 Date of first biopsy

Refers to the date of first biopsy conducted (e.g. fine needle aspiration cytology (FNAC), core biopsy, others).

4.4.14.5 Date of histology report

Refers to the date of the pathology report confirming malignancy.

4.4.14.6 Date of diagnostic resolution

Refers to the date of when the diagnosis was made known to the patients.

4.4.14.7 Date of initial treatment

Refers to the date of starting the first treatment.

4.4.15 Study Instruments

The instrument used to measure associated factors and outcomes in this study was a self-devised questionnaire. The questionnaire was designed based on the research questions and objectives of the study.

At first, the relevant literature search was done on the type of delays in breast cancer. Each type of delay (presentation, diagnosis, treatment) was identified. The time intervals to measure the delay were sought. A literature search on associated factors to delays with regards to personal, socio-cultural and economic aspects were done. Then, standard questionnaires measuring delays in breast cancer were searched and adapted to this study instrument to suit the study's respondents, i.e. breast cancer patients.

The self-devised questionnaire consisted of socio-demographic, medical history, family history, symptoms and presentation details, referral details, diagnostic details, histopathology details, treatment details, treatment adherence details, and complementary and alternative medicine (CAM) use. The questionnaire was first developed in English. It was given to experts for content and face validity. Their comments and suggestions were taken into account and amendments were made accordingly. The revised questionnaire was then back translated from English to Bahasa Malaysia, and vice versa to ensure that the context and content were similar in both languages.

The study instruments was then tested for content and face validity with breast cancer survivors. Validity is the amount of systematic or built in error in measurement and reliability indicates the accuracy or precision of the measuring instrument (Norland, 1990).

4.4.15.1 Face validity

The questionnaire was tested for face validity to assess the clarity of the wording of the items. This process also aimed at checking the level of difficulty of the questions and knowing whether all questions are easily understood. To establish this process, a draft of the questionnaire was distributed to 20 breast cancer patients in UMMC which were excluded from the study. The respondents' feedback and comments on the difficulties in

understanding or ambiguous meaning of certain words or sentences were recorded. Based on the pre-test finding, the questionnaire was modified to improve the clarity of the items.

4.4.15.2 Content Validity

Content validity was performed prior to the main study. It was conducted by relying on the knowledge of experts in the area being studied. The initial draft of the questionnaire was given to 7 professional individuals comprising of 1 breast surgeon, 2 medical officers, 2 nursing academics and 2 researchers with a similar background of the study. Comments were given whether the content of the questionnaire was appropriate and relevant to the study purpose. The questionnaire was then revised based on their suggestions and comments.

4.4.15.3 Final questionnaire

The final questionnaire consisted of self-devised questionnaires, named *Breast Cancer Delay Survey* (BCDS) questionnaire (Appendix D). It was an interviewer guided questionnaire to ensure high response rate and quality data. The questionnaire was presented in a consistent manner, thus the likelihood for bias or error was almost negligible. Besides, less time and less energy were required because most items the questionnaires were close-ended questions. The interview session was conducted personally by the researcher. The details of items are described in Table 4.4.

Table 4.3: Summary components of questionnaire for each interval

	Component of Questionnaire	Presentation interval	Diagnosis interval	Treatment interval
Self – devised	a) Socio-demography	√	√	√
	b) Medical, obstetrics and gynaecology history	√	√	√
	c) Family history in breast cancer	√	√	√

d)	Symptom and presentation details	√		
e)	Referral details		√	
f)	Diagnostic and report details		√	
g)	Histopathology and staging details		√	
h)	Breast cancer treatment details			√
i)	Treatment adherence			√
j)	Complementary and alternative (CAM) treatment use	√	√	√

4.4.16 Components of the questionnaire

(a) ***Socio-demography***

This section consists of questions on the basic socio-demographic characteristics, including respondent's age, ethnicity, religion, marital status, place of residence, educational level, working status, working sector, reason to leave job, household income and living arrangements.

(b) ***Medical, obstetrics and gynaecology history***

This section consists of questions on the medical history, including disease (i.e. hypertension, diabetes mellitus, heart disease, psychiatric disorder, kidney problem, others), history of benign breast disease, pregnancies, parity, breastfeeding, menarche, menopause, hormone replacement therapy, alcohol, smoking and contraception.

(c) ***Family history in breast cancer***

This section gathered information about family history with breast cancer, including number of family members with breast cancer, level of family member and number of family members died due to breast cancer.

(d) ***Symptom and presentation details***

This section consists of questions on the symptom duration, type of breast cancer symptom, symptom interpretation, method of detection, Breast Self-Examination (BSE) practices and first visit to primary care.

(e) ***Referral details***

This section consists of questions on the referral details, including the referral type, date of appointment, type of diagnostic center and date of first consultation at diagnostic centre.

(f) ***Diagnostic and report details***

This section consisted of questions on diagnostic details, including the type of biopsies, date of biopsies, date of pathology report and pathology details. In addition, details on location of diagnosis, date of diagnosis resolution and date of diagnosis informed to patient were obtained. Meanwhile, the breast examination such as imaging (i.e. mammogram and ultrasound) and staging test (i.e. chest x-ray, liver function test, CT scan, and bone scan) were also taken.

(g) ***Histopathology and staging details***

This section consists of questions on the histopathology details, including the cancer locality, histology, grade, lymph node, estrogen receptor, progesterone receptor and cancer stage.

(h) ***Breast cancer treatment details***

This section consists of the questions on the breast cancer details, including the surgery, chemotherapy, radiotherapy and hormonal therapy. All details regarding the start and end dates of treatment, treatments location, treatment procedure and status were reviewed.

(i) ***Adherence to breast cancer treatments***

This section consists of the questions on the adherence status of breast cancer treatments, including surgery, chemotherapy, radiotherapy and hormonal therapy. Adherence to hormonal therapy and reasons for non-adherence to treatments were obtained from the patients.

(j) ***Complementary and alternative medicine (CAM)***

This section consists of questions on the CAM use; type of CAM, time of CAM use, the number of CAM and cost of CAM.

4.4.16 Informed Consent

Informed consent is the subject agreement to take part voluntarily in the study. Consent was retrieved after patients were informed and understood the aim of the study, which was prior to data collection. In this study, patients were informed about the research purposes, interview procedures and the rights to willingly consent or refuse to participate in the study. They can withdraw participation at any time of the interview and were assured that there were no possibilities of risks or costs encountered.

Privacy and confidentiality of the patients were maintained throughout the study. In this study, privacy was maintained by not disclosing the patient's name and other identifiers on the questionnaire and research reports. The written consent form was detached from the questionnaire before the data entry and analysis. The questionnaires were only numbered after the data were collected. Patients were treated as independent subjects and no pressure was placed on them to participate. Information about the researcher name, full address, phone number and email address were provided in the event of further questions or complaints. Confidentiality was also assured during data processing and when reporting or publishing the study.

4.4.17 Data Processing

Data processing in this study involved editing, coding, classifying, tabulating and charting and diagramming of data. Data processing had successfully removed the irrelevant data to establish a better arrangement of the dataset and altogether giving shape to the mass of data. Firstly, the editing was done by examining the raw data in the questionnaires and environmental survey checklist to detect errors and omissions. Then, the errors were corrected to ensure that they were ready for the data entry. Before the data entry, the coding of the data was done. The coding of the variables is critical for a better interpretation of the result and the researcher can directly key in the code from the questionnaires. Subsequently, the raw and coded data were keyed into the database software of Statistical Package of Social Science software (SPSS Inc., Chicago) for windows version 20. Data cleaning was conducted upon the completion of data entry, by spot-checking, eyeballing and logic checking. Before the analysis of the data was conducted, the scatter-plot against the case number was performed to identify the data that were out of range.

4.4.18 Data Analysis

Data analysis was conducted by using Statistical Package for Social Sciences software (SPSS Inc., Chicago) version 20. A descriptive analysis was initially utilized to summarize the large set of data. Demographic characteristics of the respondents were tabulated and compared. The parameters of median (range) were used to describe continuous variables and parameters of frequency (%) for categorical variables. All numerical variables were tested for normal distribution with the Kolmogorov-Smirnov goodness-of-fit test to allow appropriate statistical tests. The interval distributions were highly skewed because of a few extremely long intervals. Therefore, we compared medians rather than means to give a more accurate picture of the true distributions

The time intervals of presentation, diagnosis and treatment were then divided into dichotomous outcome; delay and non-delay by using 3 months, 1 month and 1 month cut-off points respectively. Factors affecting delays in breast cancer were then identified through univariate analysis. Univariable logistic regression was conducted to look at the strength of the association between outcomes (presentation delay, diagnosis delay and treatment delay) with each factor of interest. Results were presented as crude odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant.

The analyses were then continued by using multivariable logistic regression to identify the factors associated with delays in presentation, diagnosis and treatment of breast cancer. All factors of interest were included and adjusted with other covariates. A stepwise backward selection procedure was used when selecting significant variables in the model. The interaction terms and multicollinearity problem of the final model were checked. The final model was tested for fitness using the Hosmer-Lemeshow goodness of fit test. Results were presented as adjusted odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant.

Treatment adherence was also divided into dichotomous outcome; adherence and non-adherence. An analysis was conducted to determine the association between non-adherence to treatments and its associated factors. The univariable and multivariable logistic regression model were used to estimate the associated factors to non-adherence. Results were presented as crude and adjusted odds ratios (OR) respectively, 95% confidence interval (CI) and p value <0.05 was considered as significant.

4.4.19 Operational definitions

There are two types of variables; independent and dependent variables. The independent variables encompass the variables that were operated by the researcher, and the dependent variables were the responses measured in the study; presentation delay, diagnosis delay, treatment delay and non-adherence to breast cancer treatments (e.g:

surgery, chemotherapy, radiotherapy, hormonal therapy). All variables that were used in this study based on their operational definition are as follows.

Dependent Variables

(a) ***Time intervals between important time points in the breast cancer journey***

i. Presentation interval: The time taken for present to a primary care facility.

ii. Referral interval: The time taken for referral to a diagnostic centre

iii. Biopsy interval: The time taken to do a biopsy

iv. Report interval: The time taken for a pathology report of confirmed malignancy

v. Disclosure interval: The time taken to a diagnostic resolution.

vi. Diagnosis time: The time taken from presentation at primary care to a diagnostic resolution.

vii. Treatment time: The time taken from diagnostic resolution to initiation of first treatment.

(b) ***Breast cancer delay***

i. Presentation delay: Presentation interval of more than 3 months.

ii. Diagnosis delay: Diagnosis interval of more than 1 month (30 days).

iii. Treatment delay: Treatment interval of more than 1 month (30 days).

(c) ***Stage of diagnosis***

The breast cancer staging as referred to the American Joints Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition (Edge et al., 2010) are as below;

i. Early stage: Breast cancer patients diagnosed at Stage I and II.

ii. Late stage: Breast cancer patients diagnosed at Stage III and IV.

(d) ***Adherence of breast cancer treatments***

i. Adherence: Any breast cancer patients undergoing treatment or stopping due to medical reasons.

ii. Non-adherence: Any breast cancer patients refusing, incomplete, or discontinuing treatments due to non-medical reasons.

Independent variables

(a) ***Socio-demographic characteristic***

i. Age: Age at diagnosis, calculated from the date of birth and date of diagnosis.

ii. Ethnicity: Malay, Chinese, Indian or Others.

iii. Religion: Islam, Buddhism, Hinduism, Christianity, Others

iv. Marital Status: Single, married, divorced or widowed, unknown.

v. Education: Highest education level achieved by the patient; primary, secondary, tertiary

vi. Household income: The combined gross income of all the members of a household who are working, in Ringgit Malaysia (RM).

vii. Employment status: Working, used to work, not working.

viii. Work sector: Public, private, self-employed.

ix. Reason from stopping work: Because of breast cancer, not because of breast cancer

x. Living arrangement: Currently living with husband, children, alone, family member, parents, friends

(b) ***Medical history and obstetric details***

i. Medical history: History of medical background; hypertension, diabetes mellitus, heart disease, psychiatric disorder, kidney problem, others.

ii. History of benign breast cancer: Yes, No

iii. Parity status: Nulliparous, parous

iv. Number of pregnancies

v. Breastfeeding (ever): Yes, no or unknown

vi. Menarche: Age at first menstrual cycle experienced by the patient

vii. Menopausal (Yes) : Age when menstrual periods stop permanently

viii. Alcohol (ever): Yes, no or unknown

ix. Smoking (ever): Yes, no or unknown

x. Contraception: Contraception either pills or injection either yes, no or unknown

(c) ***Family history and previous experiences with breast cancer***

i. Family with breast cancer: Yes, no or unknown

ii. Level of family member affected by breast cancer: First degree (e.g. mother, sister, daughter), second degree (e.g. aunt, grandmother) or third degree (e.g. niece, cousin)

iii. Side of family member: maternal or paternal.

(d) ***Patient symptom and presentation details***

i. First cancer symptom: Type of symptom/s experienced by the patient before present to medical care; lump, breast pain, shape changes, nipple problem, rashness, asymptomatic and others.

ii. Detection method: Method of cancer detection either through symptom-detected (e.g. breast self-examination, clinical breast examination) and screen-detected (e.g. mammogram, ultrasound).

iii. Primary care facility: Type of primary care service visited by the patient either through the private clinic (e.g. general practitioner), public clinic (e.g. *klinik kesihatan*), out-patient department (OPD), accident and emergency (A&E) (Allgar & Neal, 2005) after discover symptom or any breast abnormalities.

iv. Diagnostic centre: Type of secondary care service visited by the patient for the first time either through the surgery out-patient department (SOPD) or breast clinic.

(e) ***Diagnostic details***

i. Type of biopsy: Method of biopsy underwent by the patient for diagnosis. Consisting of needle (fine needle aspiration cytology, core needle biopsy, ultrasound guided) and surgical (incision, excision) biopsy.

ii. Diagnosis location: Location of diagnosis was performed either at participating hospitals or other hospitals

iii. Date of diagnosis: Date of histopathological report

iv. Date of diagnostic resolution: Date of when the diagnostic resolutions are made known to the patients.

(f) ***Histopathology and staging details***

i. Cancer site: Affected breast site either right, left or both

ii. Histology type: Histological appearance of the breast cancer classification

iii. Tumor size (cm): Measured at the widest tumor points, diameter.

iv. Grade: Bloom Richardson grading appearance of the breast cancer cells compared to the appearance of normal breast tissue either well differentiated (low grade/ grade 1), moderately differentiated (intermediate grade/ grade 2), poorly differentiated (high grade/ grade 3)

v. Stage: Referring to the American Joints Cancer Committee (AJCC), 7th edition staging using the TNM system (Edge et al., 2010). Size of the tumor (T), spread to the lymph nodes (N), tumor metastasis (M).

(g) ***Breast cancer treatment***

i. Treatment status: Eligibility for breast cancer treatment

ii. Treatment location: Location of where treatment was performed either at selected hospital or other hospitals

iii. Treatment date: Date of breast cancer treatment

iv. Treatment procedure: Type of treatment underwent by the patient either surgery (e.g. mastectomy, breast conversing surgery), chemotherapy, radiotherapy and hormonal therapy.

v. Treatment adherence: Treatment status either adherent or non-adherent

4.5 Results

The results of the study are divided into 5 parts which based on the study objectives:

1. Descriptive statistics on the characteristics of breast cancer patients.

2. The time intervals taken between important time points in the breast cancer journey from symptom discovery to initial treatment.

3. The proportions of delays in presentation, diagnosis and treatment of breast cancer.

4. Univariate and multivariate analysis of factors associated with delays in presentation, diagnosis and treatment of breast cancer.

5. The proportions and factors associated with non-adherence in breast cancer treatments.

4.5.1 Background profile of respondents

Respondents for this study were recruited from six tertiary public hospitals in Malaysia which covers four states in Peninsular Malaysia and one state in East Malaysia. All of these hospitals are the main hospital in each area and serves as a referral hospital for the breast cancer patients.

A total of 870 breast cancer patients were registered at these hospitals and were diagnosed between 1st January and 31st December 2012. From this number, only 420 medical records were successfully obtained. All patients with medical records were then reviewed and contacted for informed consent. This study primarily concerned with newly diagnosed breast cancer and the time evaluation, resulting 80 patients were removed from the study due to the following reasons: recurrent breast cancer (n=25), diagnosed with other cancer (n=15), refused to participate (n=20), and incomplete dates (n=20). Therefore, the final sample size was 340 patients giving a response rate of 39%.

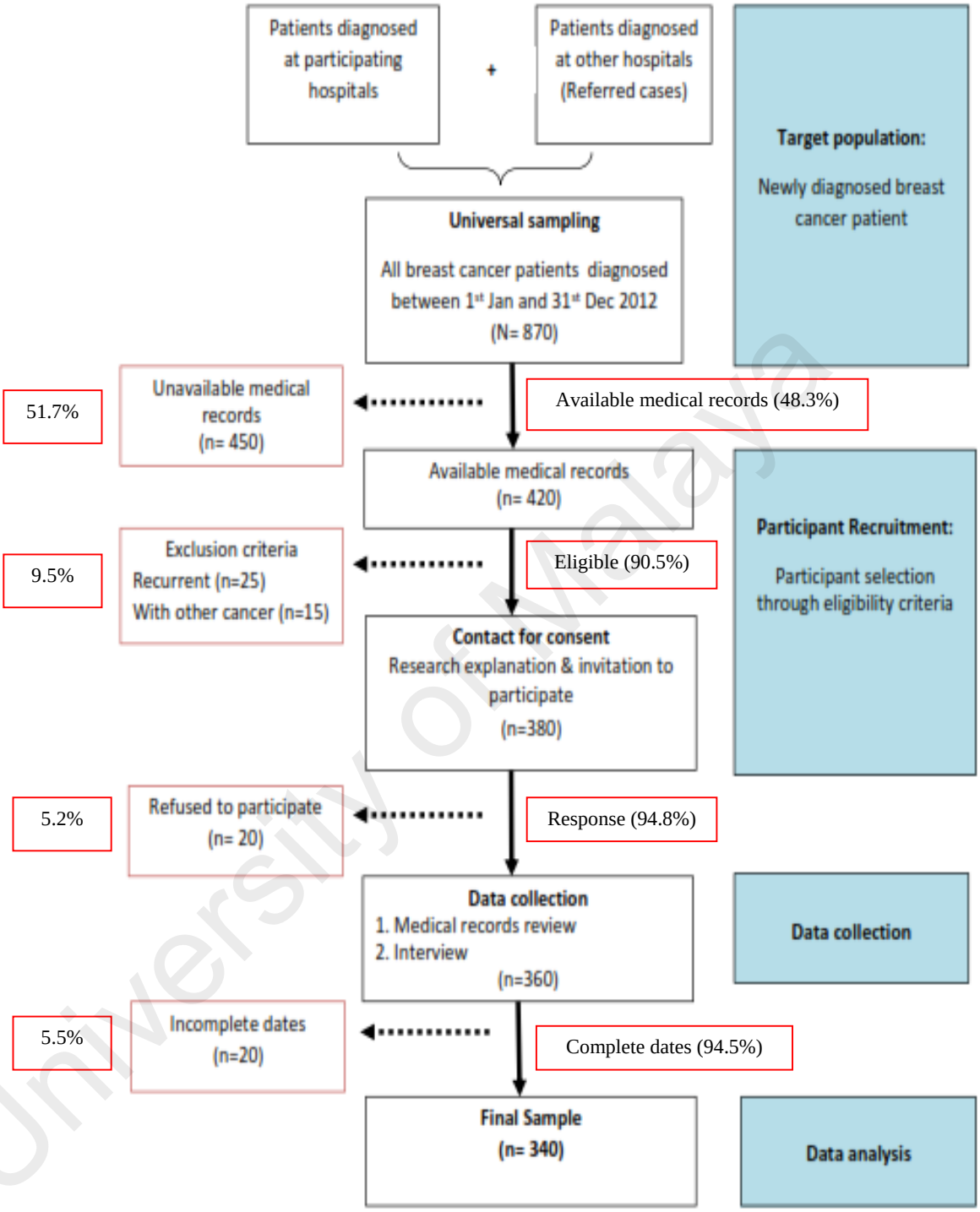


Table 4.4: Sampling procedure flow chart

4.5.2 Justification of final sample size

Patients selected in this study were based on the medical records availability and researcher had no control over this. Most of the medical records failed to be traced despite after three requests made. From 870, 450 (51.7%) patients failed to be traced. The unavailability of medical records was caused because they were being used by doctors or other hospital departments.

All patients with medical records were then reviewed for eligibility. However, from 420, 40 (9.5%) patients were excluded due to exclusion criteria; recurrent breast cancer (n=25) and diagnosed with other cancer (n=15).

Then, all eligible patients with medical records were contacted for consent prior to data collection. Since the study participation was voluntary in nature and patients could withdraw participation at any time, 20 patients (5.2%) were refused to participate the study with the following reasons; not interested (n=5), busy (n=4), not allowed by family members (n=4), not answering call (n=4) and changed phone number (n=3).

To ensure for data accuracy and validity, all dates were then cross-validated between the medical records and patient interviews by the researcher. Since this study was primarily concerned with the time evaluation and each time points were important, 20 patients (5.5%) without all important dates were removed from the study.

Referring to Naing et al. (2006), a sample size must be practical to achieve based on the budget, manpower, management and the study period. Therefore, due to several limitations, only 340 patients were included in the study.

4.5.3 Number of respondents by study locations

The total number of breast cancer patients at all 6 public hospitals during the study period was 870. Maximum efforts were made to get the highest number of samples. However, due to the limitations mentioned previously, only 340 (39%) patients were successfully obtained. The numbers of patients obtained for each hospital were not similar. The patients' percentage obtained from each hospital was from 30% to 74% (refer Table 4.5).

The discrepancies of number and percentage between the hospitals were related to the non-randomized sampling conducted in this study, whereby the probability of selection cannot be accurately determined. The sample gathered in this study does not give all the individuals equal chances of being selected, thus causing an uneven patient percentage among the hospitals.

Table 4.5: Number of breast cancer patients obtained by study locations

Participating hospitals	Location	Number of total patients (N)	Number of patients obtained (n)	Percentage (%)
UMMC	Kuala Lumpur (1)	325	100	30.7
HKL	Kuala Lumpur (2)	230	80	34.7
HRPB	Ipoh, Perak	80	48	60.0
HSI	Johor Bahru, Johor	68	50	73.5
HRPZ	Kota Bharu, Kelantan	67	20	29.8
HUS	Kuching, Sarawak	100	42	42.0
	Total	**870**	**340**	**39.1**

Descriptive statistics

Patients for this study were recruited from six public hospitals in Malaysia, covering six tertiary hospitals in Kuala Lumpur, Perak, Johor, Kelantan and Sarawak. All 340 breast cancer patients were then summarized in descriptive statistic.

4.5.4 Health system details

Table 4.6 shows the distribution of public cancer services received by the breast cancer patients in these major referral centres. Majority (80%, n=272) breast cancer patients had in-house oncology services. A small proportion (20%, n=68) of patients attending public hospitals did not have resident oncologist or radiotherapy services. From the number, 8.2% (n=28) were referred to other hospitals for oncology services and 2.1% (n=7) patients received chemotherapy in the same hospital without resident oncologists.

More than half (58.8%, n=200) of the patients were attended by dedicated breast surgical services and a large remaining proportion (41.2%, n=140) of patients were attended by general surgeons.

Table 4.6: Clinical services received by the breast cancer patients in the six (6) public hospitals

Characteristic	N		n (%)
Hospital with oncology services	340	Yes	272 (80.0)
		No	68 (20.0)
Hospital surgeon	340	Breast surgeon	200 (58.8)
		General surgeon	140 (41.2)

4.5.5 Socio-demographic and histopathology characteristics of breast cancer patients

In total, 340 respondents were included in the final analysis. Table 4.7 shows the socio-demographic characteristics of the respondents. The median age of the breast cancer patients was 53 years and the age distribution ranged from 23 to 74 years old. Approximately, 38.8% were less than 50 years old and 41.8% were premenopausal.

Based on this study, the highest proportion of patients was Malays (45.3%), followed by Chinese (30.6%), Indian (15.9%) and others (8.2%). Most patients were Muslims (45.6%), followed by Buddhists, Hindus, Others and Christians.

Majority (76.2%) of the patients were married. Approximately, 57 patients were single, 14 patients were divorcees while 10 patients were widows. Most of the patients had education up to secondary school (75.9%), followed by patients with tertiary education (14.4%) and patients with primary education (9.7%).

The median household income was RM2803 per month and ranged from RM900 to RM5560. Majority of the patients (71.7%) earned less than RM3000 per month. For occupation status, 32.1% of patients were employed, 44.1% used to work and 23.8% were unemployed. Among those who used to worked, 97 (64.7%) patients left their jobs after being diagnosed with breast cancer and the remaining were due to retirement.

Table 4.7: Socio-demographic characteristic of breast cancer patients

Characteristic	N		n (%)
Age (years)	340	Mean (SD)	53.1 (11.07)
		Median (Range)	53 (23-74)
		≤ 50 years	132 (38.8)
		> 50 years	208 (61.2)
Ethnicity	340	Malay	154 (45.3)
		Chinese	104 (30.6)
		Indian	54 (15.9)
		Others	28 (8.2)
Religion	340	Islam	155 (45.6)
		Buddhism	93 (27.4)
		Hinduism	46 (13.5)
		Christianity	17 (5.0)
		Others	29 (8.5)
Marital status	340	Married	259 (76.2)
		Single	57 (16.8)
		Widowed/Divorced	24 (7.1)
Education	340	Tertiary	49 (14.4)
		Secondary	258 (75.9)
		Primary	33 (9.7)
Household income per month (RM)	340	Mean (SD)	2803 (842)
		Median (Range)	2900 (900-5560)
		< 3000	244 (71.8)
		≥ 3000	96 (28.2)
Working status	340	Employed	109 (32.1)
		Used to work	150 (44.1)
		Unemployed	81 (23.8)
Used to work	150	Leave job after diagnosis	97 (64.7)
		Retired	53 (35.3)

4.5.6 Co-morbidities and medical history of breast cancer patients

Table 4.8 shows the co-morbidities and medical history of the respondents. Approximately, 21.2% (n=72) had hypertension, 10.6% (n=36) had diabetes mellitus and 5.3% (n=18) had heart diseases. Several had a previous psychiatric disorder (n=9) and kidney problems (n=7). Only 10.3% (n=35) had experienced benign tumours before being diagnosed with breast cancer.

A large number of respondents were parous (81.6%, n=278). The median number of children was 3 (range: 1-11 children). Breastfeeding data were taken and shows majority (72.1%, n=204) of parous breast cancer patients had breastfed their children. Duration of breastfeeding was calculated for all children and the median breastfeeding duration was 9 months and ranged from 1 to 50 months.

About 14.1% (n=48) of patients had started menstruating early at the age of less than 11 years old. The median menarche age was 12 years and ranged from 9 to 15 years. Approximately, 58.2% (n=198) were post-menopausal and of these patients, only 9.6% (n=19) experienced menopause at the age of less than 50 years. The median menopausal age was 52 years old and ranged from 45 to 61 years of age.

There was a small proportion of 12.1% (n=41) consuming alcohol, 15.9% (n=54) ever-smoked and 26.2% (n=89) patients had used contraception (oral: 63, injection: 18, implant: 8). Meanwhile, almost half of the patients (46.5%, n=158) had used complementary and alternative medicine after discovering breast cancer symptom/s.

Table 4.8: Medical and obstetric history of breast cancer patients

Characteristic	N		n (%)
Medical history	340	Hypertension	72 (21.2)
		Diabetes Mellitus	36 (10.6)
		Heart disease	18 (5.3)
		Psychiatric disorder	9 (2.6)
		Kidney problem	7 (2.0)
History of benign breast disease	340	No	305 (89.7)
		Yes	35 (10.3)
Parity	340	Parous	278 (81.8)
		Nulliparous	62 (18.2)
No. of children	278	Mean (SD)	3.4 (1.5)
		Median (Range)	3 (1-11)
Breast feeding	278	Yes	204 (73.4)
		No	74 (26.6)
Total breast feeding duration (months)		Mean (SD)	12.3 (10.6)
		Median (Range)	9 (1-50)
Menarche age (years)	340	Mean (SD)	11.9 (1.4)
		Median (Range)	12 (9-15)
		< 11 years	48 (14.1)
		≥ 11 years	292 (85.9)
Menopause age (years)	198	Mean (SD)	52.7 (3.2)
		Median (Range)	52 (45-61)
		< 50 years	19 (9.6)
		≥ 50 years	179 (90.4)
Alcohol	340	No	299 (87.9)
		Yes	41 (12.1)
Ever smoked	340	No	286 (84.1)
		Yes	54 (15.9)
Contraception	89	Oral	63 (70.8)
		Injection	18 (20.2)
		Implant	8 (8.9)

Complementary and alternative medicine (CAM) use	340	Yes No	158 (46.5) 182 (53.5)

4.5.7 Family history with breast cancer

Table 4.9 shows the data of family history with breast cancer. Findings shows a small proportion of 18.2% (n=62) patients had family history of breast cancer. Approximately, 66.1% (n=41) patients had experienced breast cancer in first degree family members, 29.0% (n=18) in second degree family members and 4.8% (n=3) in third degrees family members.

Table 4.9: Family history and previous experiences with breast cancer

Characteristic	N		n (%)
Experiences breast cancer in family members	340	No Yes	278 (81.8) 62 (18.2)
Degree of family member with breast cancer	62	First degree Second degree Third degrees	41 (66.1) 18 (29.0) 3 (4.8)

*First degree: Mother, sister, daughter
*Second degree: Auntie, grandmother
*Third degree: Cousin, Niece

4.5.8 Patient presentation details

Table 4.10 shows the patients' presentation details. All 340 patients were symptomatic and none were screen-detected. Approximately, 65.3% (n=222) had performed BSE at home. The appearance of a breast lump was the most common first symptom with 88.2% (n=300) and 11.8% (n=40) presented first symptom with other than breast lump. Symptoms other than breast lump experienced by the patients were breast pain (n=10), changes of breast shape (n=9), nipple discharge (n=8) and systemic symptoms e.g. loss of weight (n=7), loss of appetite (n=6).

Approximately, 86.2% (n=293) went to the primary care facilities either through private clinics (n=197, 57.9%) and public clinic (n=96, 28.2%). Meanwhile, 13.8% (n=47) went directly to the hospital either through outpatient department (OPD) (n=32, 9.4%), accident and emergency (A&E) (n=7, 2%) and referred during admission for other diagnoses (n=8, 2.4%).

Some 88.5% (n=301) had disclosed their symptom to another person and 36.8% (n=125) of patients in this study interpreted their symptoms as non-cancerous.

Table 4.10: Symptom and presentation details of breast cancer patients

Characteristic	N		n (%)
Detection method	340	Symptom detection	340 (100)
		Screen detection	0 (0)
Performed breast self-examination (BSE)	340	Yes	222 (65.3)
		No	118 (34.7)
First symptom	340	Breast lump	300 (88.2)
		Other than breast lump	40 (11.8)
First symptoms other than breast lump	40	Systemic symptoms	13 (32.5)
		Breast pain	10 (25.0)
		Changes of breast shape	9 (22.5)
		Nipple discharge	8 (20.0)
First presentation at primary care facility	340	Primary care facility	293 (86.2)
		Private clinic (e.g. GP)	197 (57.9)
		Public clinic (e.g. KK)	96 (28.2)
		Direct to hospital	47 (13.8)
		Out-patient department (OPD)	32 (9.4)
		Accident & Emergency (A&E)	7 (2.0)
		Admitted for other diagnoses	8 (2.4)
Disclosed symptom to others	340	Yes	301 (88.5)
		No	39 (11.5)
Symptom interpretation	340	Cancerous	215 (63.2)
		Non-cancerous	125 (36.8)

*GP= general practitioner, KK= klinik kesihatan

4.5.9 Diagnostic details

Table 4.11 shows the diagnosis and biopsy details of the breast cancer patient. Majority, 83.5% (n=284) patients were diagnosed with breast cancer at the studied hospital, while 16.5% (n=56) patients were diagnosed at other hospitals and referred for treatments. Mostly, it took only one biopsy to confirm the diagnosis and the number could range from 1 to 4 biopsies. Approximately, 68.8% (n=234) were diagnosed with 1 biopsy and 31.2% (n=106) were diagnosed with 2 or more biopsies.

Majority (83.2%, n=283) of patients were diagnosed by needle biopsy. Needle biopsy were those who were diagnosed through FNAC (16.5%, n=56), core biopsy (50%, n=170) and ultrasound image guided core biopsy (16.7%, n=57).

Meanwhile, a small number (16.8%, n=57) of patients were diagnosed by surgical biopsy. Surgical biopsy were those who were diagnosed through excisional biopsy (15.3%, n=52) and incisional biopsy (1.5%, n=5). From this number, 50 patients underwent at least one core biopsy before a surgical biopsy.

Table 4.11: Diagnostic details of breast cancer patient

Characteristic	N		n (%)
Place of diagnosis	340	Studied hospitals	284 (83.5)
		Other hospitals	56 (16.5)
Number of biopsies (needle and surgical)	340	Median (Range)	1 (1-4)
		1 biopsy	234 (68.8)
		≥ 2 biopsies	106 (31.2)
Type of final biopsy of confirmed malignancy	340	Needle	283 (83.2)
		Surgical	57 (16.8)
Type of needle biopsy	283	FNAC	56 (16.5)
		Core needle biopsy	170 (50.0)
		US image guided core biopsy	57 (16.7)
Type of surgical biopsy	57	Excisional biopsy	52 (15.3)
		Incisional biopsy	5 (1.5)

*FNAC=fine needle aspiration cytology, US=ultrasound

4.5.10 Cancer characteristics of the breast cancer patients

Table 4.12 shows the data on histopathology findings of the respondents. All patients (100%) had a pathology report confirming malignancy. Half (50.3%, n=171) cases occurred at the right breast, 47.4% (n=161) at the left breast and 2.4% (n=8) at both breasts. Grade 2 showed the highest number with 36.2%, followed by grade 3 (28.2%) and grade 1 (11.8%). All patients were staged according to the TNM American Joints Cancer Committee (AJCC) Classification. About 17.4% were diagnosed at stage I, 37.6% diagnosed at stage II, 33.5% diagnosed at stage III and 11.5% diagnosed at stage IV. This means, 55% of patients were diagnosed with early stage breast cancer (stage 1 & 2) and 45% with late stage breast cancer (stage 3 & 4). Estrogen receptor (ER) and progesterone receptor (PR) status showed that approximately, 54.1% were ER+ and 50.3% were PR+.

Table 4.12: Cancer histopathology characteristic of the breast cancer patients

Characteristic	**N**		**n (%)**
Site	340	Right	171 (50.3)
		Left	161 (47.4)
		Bilateral	8 (2.4)
Grade	340	1	40 (11.8)
		2	123 (36.2)
		3	96 (28.2)
		Unknown	81 (23.8)
Stage	340	I	59 (17.4)
		II	128 (37.6)
		III	114 (33.5)
		IV	39 (11.5)
Estrogen receptor	340	Positive	184 (54.1)

		Negative	142 (41.8)
		Unknown	14 (4.1)
Progesterone receptor	340	Positive	171 (50.3)
		Negative	150 (44.1)
		Unknown	19 (5.6)

4.5.11 Treatments of breast cancer patients

Table 4.13 shows the data on treatments of the respondents. Surgery is the mainstay of breast cancer treatment and is highly accessible at public hospitals in Malaysia. From 329 (96.7%) patients who were recommended for surgery, 283 (86%) adherence to surgery, with 165 (77.1%) underwent mastectomy (MAC), 9 (4.2%) underwent mastectomy (MAC) and breast reconstruction, and 109 (94.8%) underwent breast conserving surgery (BCS).

From 243 (71.5%) patients who were recommended for chemotherapy, 170 (69.9%) adherence to chemotherapy, with 145 (71.1%) underwent adjuvant chemotherapy and 25 (64.1%) underwent neo-adjuvant chemotherapy.

Meanwhile, from 210 (61.7%) patients who were recommended for radiotherapy, 140 (66.7%) adherence to radiotherapy. From 193 (56.7%) patients who were recommended for hormonal therapy, 123 (63.7%) adherence to hormonal therapy after 1 year of diagnosis. Approximately, 103 (63.6%) were prescribed with tamoxifen and 20 (64.5%) were prescribed with aromatase inhibitors.

Table 4.13: Proportion patients' adherent to breast cancer treatments

Treatments	Recommended for treatment (N)	Adherence rate n (%)
Surgery	329 (96.7)	283 (86.0)
Mastectomy (MAC)	205 (60.3)	165 (77.1)
Mastectomy (MAC) and reconstruction	9 (2.6)	9 (100)
Breast conserving surgery (BCS)	115 (33.8)	109 (94.8)
Chemotherapy	243 (71.5)	170 (69.9)
Adjuvant	204 (60.0)	145 (71.1)
Neo-adjuvant	39 (11.5)	25 (64.1)
Radiotherapy	210 (61.7)	140 (66.7)
Hormonal therapy	193 (56.7)	123 (63.7)
Tamoxifen	162 (47.6)	103 (63.6)
Aromatase inhibitors	31 (9.1)	20 (64.5)

Hormonal therapy: at 1-year after diagnosis
Recommended for treatment: N/340 patients; Adherence rate: n/N

4.5.12 Non-adherence to treatments in breast cancer patients

Table 4.14 summarizes the non-adherence status for the breast cancer treatment; surgery, chemotherapy, radiotherapy and hormonal therapy among the breast cancer patients attending public hospitals in Malaysia.

From 329 patients who were recommended for surgery, 46 (14%) were non-adherence to surgery, with 40 (18.7%) failed to underwent mastectomy (MAC) and 6 (5.2%) failed to underwent breast conserving surgery (BCS).

From 243 patients who were recommended for chemotherapy, 73 (30%) were non-adherence to chemotherapy, with 59 (28.9%) failed to undergo adjuvant chemotherapy and 14 (35.8%) failed to undergo neo-adjuvant chemotherapy.

From 210 patients who were recommended for radiotherapy, 70 (33.3%) were non-adherence to radiotherapy. Meanwhile, from 193 patients who were recommended for hormonal therapy, 70 (36.3%) were non-adherence to hormonal therapy at 1 year after diagnosis. Approximately, 59 (36.4%) failed to adhere to tamoxifen out of 162 patients and 11 (35.5%) out of 31 patients who recommended aromatase inhibitors failed to consume aromatase inhibitors.

Table 4.14: Proportion patients' non-adherent to breast cancer treatments

Treatments	Recommended for treatment (N)	Non-adherence rate n (%)
Surgery	329 (97.6)	46 (14.0)
Mastectomy (MAC)	205 (60.3)	40 (19.5)
Mastectomy (MAC) and reconstruction	9 (2.6)	0 (0)
Breast conserving surgery (BCS)	115 (33.8)	6 (5.2)
Chemotherapy	243 (71.5)	73 (30.0)
Adjuvant	204 (60.0)	59 (28.9)
Neo-adjuvant	39 (11.5)	14 (35.8)
Radiotherapy	210 (61.7)	70 (33.3)
Hormonal therapy	193 (56.7)	70 (36.3)
Tamoxifen	162 (47.6)	59 (36.4)
Aromatase inhibitors	31 (9.1)	11 (35.5)

Hormonal therapy: at 1-year after diagnosis
Recommended for treatment: N/340 patients; Adherence rate: n/N

4.5.13 Reasons for non-adherence to the breast cancer treatments

Further investigations were carried out involving those who did not adhere to one or more breast cancer treatments (n=102, 30%). Results showed the reasons for non-adherence were; refusing treatments (n=49, 14.5%), incomplete or stopped treatment with non-medical reasons (n=28, 8.2%), and missed going to hospital (n= 25, 7.3%).

Table 4.15: Reasons for non-adherence for breast cancer treatments

Reasons for non-adherence	n (%)
Refusal for treatments	49 (14.5)
Incomplete or stopped for non-medical reasons	28 (8.2)
Missed going to hospital	25 (7.3)

The time intervals between important time points in the breast cancer journey from symptom discovery to initial treatment

4.5.14 The time taken to presentation, diagnosis and treatment of breast cancer

Table 4.16 summarizes the time intervals taken to presentation, diagnosis and treatment of breast cancer in Malaysia. The time intervals are reviewed from the times of symptom discovery to diagnosis and to the initial treatment. The median time to first presentation was 2.4 months and ranges from 7 days to 10 years. The median times to diagnostic resolution was 26 days and ranged from 4 days to 9.3 months.

From the total of 340 patients, 318 had undergone initial treatment while 22 patients who refused for any treatment and were excluded from treatment analysis. Therefore, the median time to initial treatment was 21 days and ranged from 1 day to 7.2 months. In general, a median time of 4.9 months is needed for a total interval of breast cancer journey from symptom discovery to initial treatment which ranges from 1 month to 10 years.

Table 4.16: The time taken to presentation, diagnosis and treatment of breast cancer patients in Malaysia

No.	Time intervals	n	Median	Range
1.	Time to presentation	340	2.4 months	7 days – 10 years
2.	Time to diagnosis	340	26 days	4 days – 9.3 months
3.	Time to initial treatment	318	21 days	1 day – 7.2 months
4.	Total interval	318	4.9 months	1 month – 10 years

*22 patients refused for any treatment

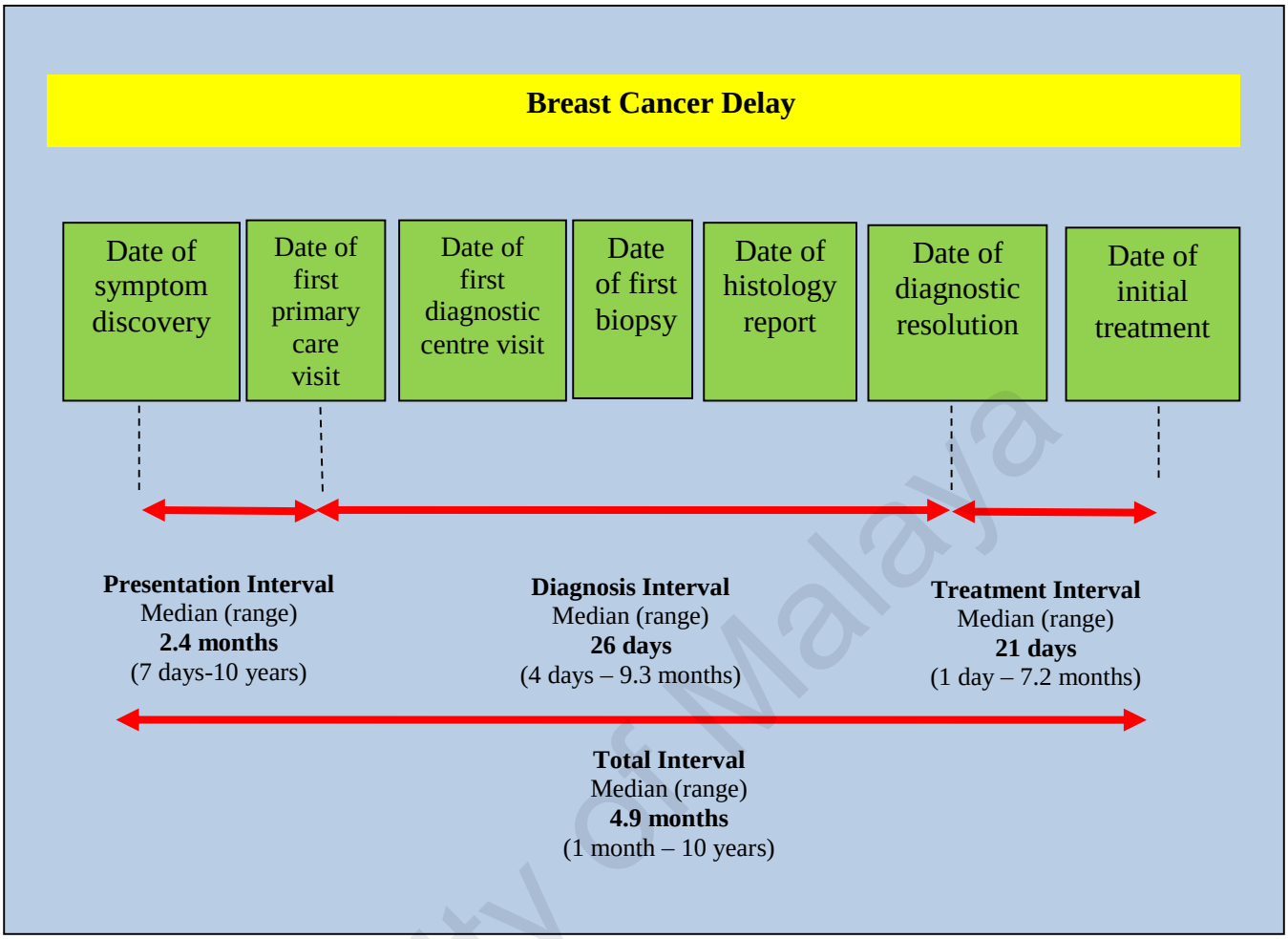


Figure 4.5: Time intervals taken to presentation, diagnosis and treatment of breast cancer in Malaysia

4.5.15 The time intervals of breast cancer diagnosis

Table 4.17 summarizes the time intervals taken to breast cancer diagnosis resolution. The time intervals are reviewed from the time to first primary care visit to the diagnostic resolution.

Referral interval was the longest time intervals in the breast cancer diagnosis. The median time for referral interval from primary care to diagnostic center was 8 days and range from 0 day (same day) to 8 months. A maximum referral interval of 8 months can be seen in a patient who refused for further investigation, resulting delayed visit to diagnostic center. In the meantime, those who were referred from a primary health care (e.g. public and private clinics) had shorter referral time compared to those who directly went to the hospitals (e.g. A&E, OPD) with the median time of 7 days and 9 days respectively.

The median time for biopsy interval from diagnostic center to first biopsy was 0 day (same day) and ranges from 0 to 20 days. Majority of patients (89%) underwent biopsy at their first visit to the diagnostic center.

From the biopsy, it took a median time of 7 days (range: 3 day – 3.5 months) to confirm a pathology report and followed by a median time of 4 days (range: 1 day – 1.8 months) for patients to know the diagnosis.

Table 4.17: The time taken to referral, biopsy, report and disclosure of breast cancer patients in Malaysia

No.	Time intervals	N	Median, days	Range
1.	Referral interval	340	8	0 day (same day) - 8months
	Primary care	293	7	
	Hospital	47	9	
2.	Biopsy interval	340	0	0 day (same day) – 20 days
3.	Report interval	340	7	3 day – 3.5 months
4.	Disclosure interval	340	4	1 day – 1.8 months

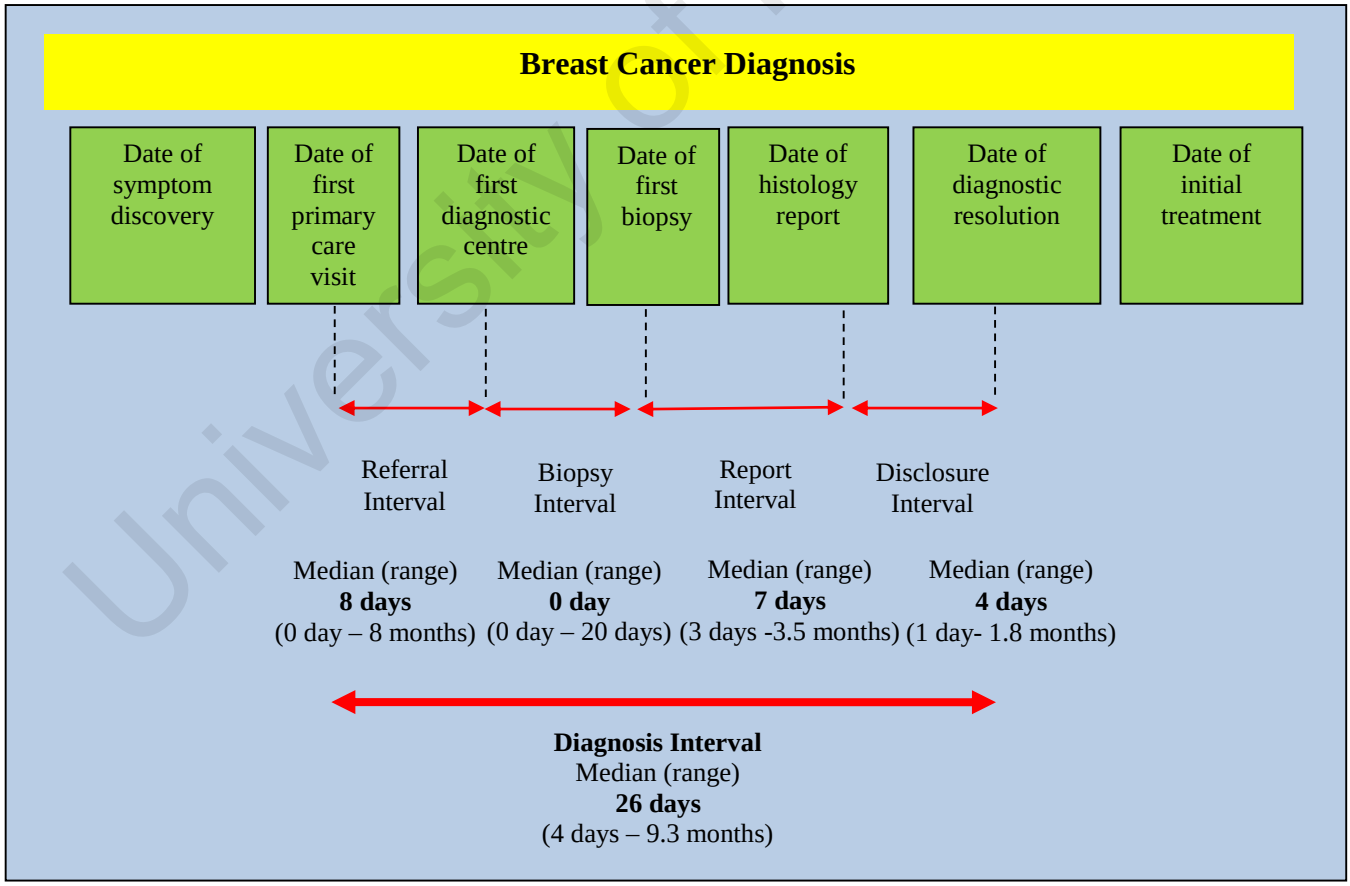


Figure 4.6: Time intervals taken to a diagnosis of breast cancer in Malaysia

4.5.16 The time intervals from diagnosis to breast cancer treatments

Table 4.18 summarizes the time taken from diagnosis to surgery, chemotherapy, radiotherapy and hormonal therapy among breast cancer patients in Malaysia. From the analysis, breast cancer surgery was highly accessible whereby 283 (86%) patients had surgery with a median time from diagnosis to surgery within 22 days and ranges from 1 day to 5.8 months.

Performance for initiation of the 3 treatment modalities; chemotherapy, radiotherapy and hormonal therapy are comparable. Some 170 (69.9%) patients had chemotherapy with a median time from diagnosis to chemotherapy of 57 days and ranges from 2 day to 8.2 months.

On the other hand, 140 (66.7%) patients had radiotherapy. The median time from diagnosis to radiotherapy was 190 days and ranged from 3.5 months to 1.1 years.

Meanwhile, 123 (63.7%) patients received hormonal therapy within 1 year of diagnosis with a median time from diagnosis to the start of hormonal therapy was 212 days and ranged from 8 days and 1.7 years.

Table 4.18: The time taken from diagnosis to treatments of breast cancer in Malaysia

No.	Time intervals from diagnosis	Underwent treatment (n)	Adherence rate (%)	Median, day	Range
1.	Surgery	283	86.0	22	1 day -5.8 months
2.	Chemotherapy	170	69.9	57	2 day – 8.2 months
3.	Radiotherapy	140	66.7	190	3.5 months – 1.1 years
4.	Hormonal therapy	123	63.7	212	8 days – 1.7 years

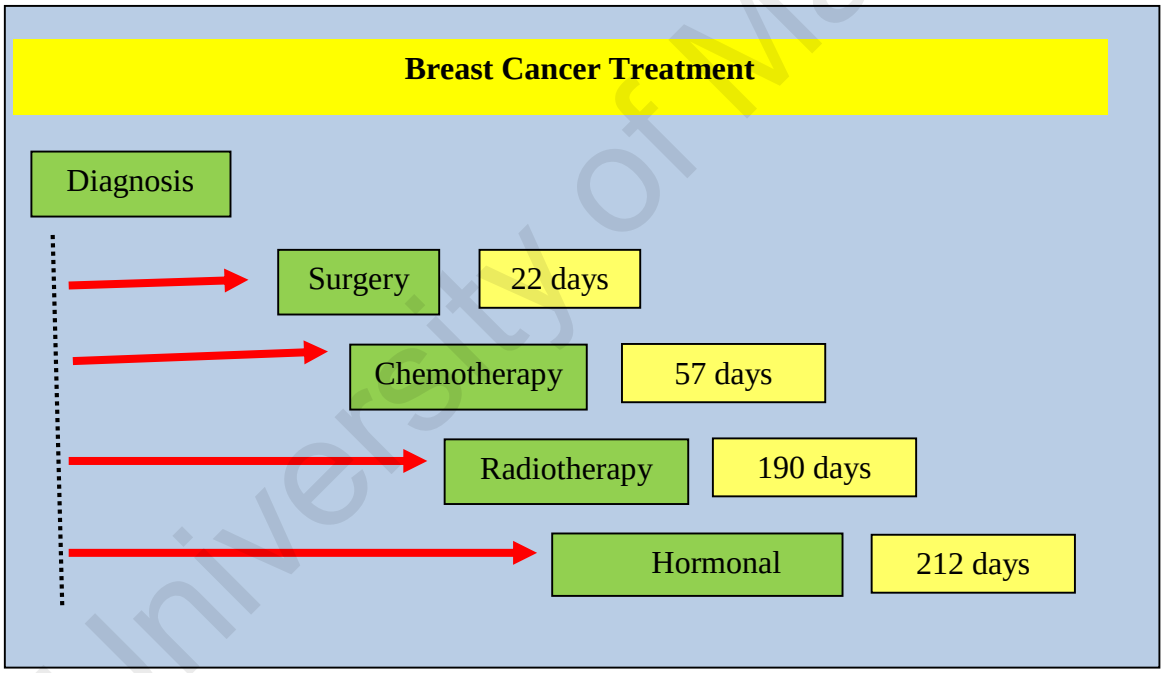


Figure 4.7: The time intervals taken from diagnosis to breast cancer treatments in Malaysia

4.5.17 The time intervals taken between the breast cancer treatments

Table 4.19 summarizes the time taken between the breast cancer treatments from diagnosis to surgery, surgery to chemotherapy, chemotherapy to radiotherapy and radiotherapy to hormonal therapy among breast cancer patients in Malaysia.

The median time from diagnosis to surgery was 22 days and ranges from 1 day to 5.8 months. The median time from surgery to adjuvant chemotherapy was 44 days and ranges from 4 days to 5.8 months. Longer interval can be seen for neo-adjuvant chemotherapy with 101 days median time and ranges from 35 days to 5.4 months.

The median time from chemotherapy to radiotherapy was 121 days and ranges from 20 days to 8.7 months. Meanwhile, the median time from radiotherapy to hormonal therapy was 37 days and ranges from 3 days to 1.2 years.

Table 4.19: The time taken between the breast cancer treatments in Malaysia

No.	Time intervals between treatments	Median, day	Range
1.	From diagnosis to surgery	22	1 day - 5.8 months
2.	From surgery to chemotherapy		
	- Adjuvant	44	4 days -5.8 months
	- Neo-adjuvant	101	35 days-5.4 months
3.	From chemotherapy to radiotherapy	121	20 days -8.7 months
4.	From radiotherapy to hormonal therapy	37	3 days – 1.2 years

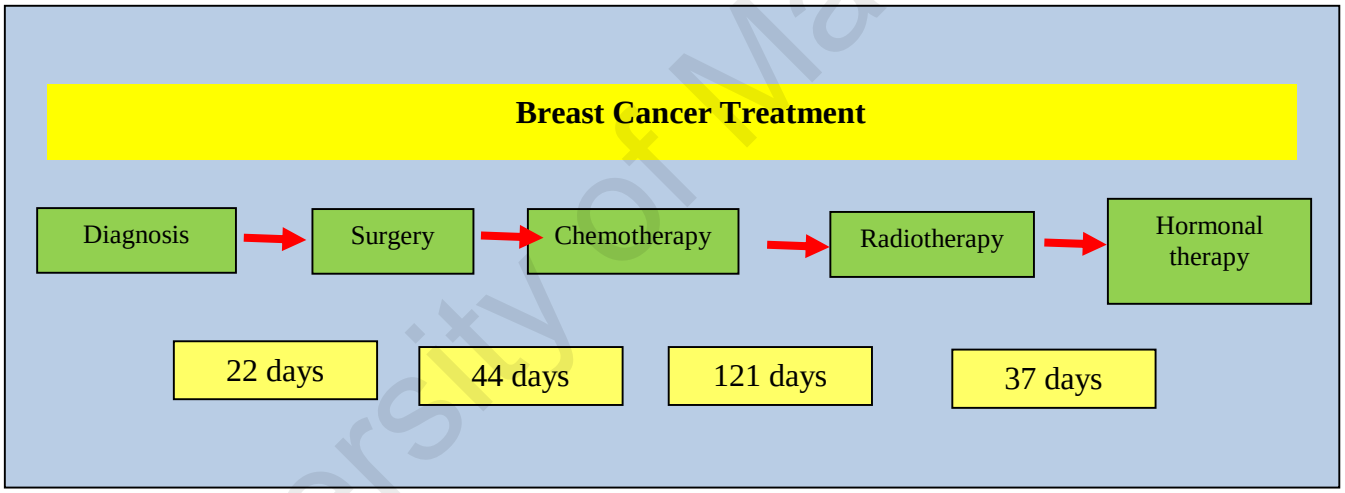


Figure 4.8: The time intervals taken between the breast cancer treatments in Malaysia

4.5.18 The proportion of delays in presentation, diagnosis and treatment of breast cancer in Malaysia

Table 4.20 summarizes the proportion of delays in presentation, diagnosis and treatment of breast cancer in Malaysia. This section analyses delay according to delays categories that were defined in Chapter 3.

The proportion of diagnosis delay shows the highest percent of 41.8% (n=142) compared to presentation delay and treatment delay. The proportions for presentation delay and treatment delay were 35% (n=119) and 35.3% (n=120) respectively.

Overall, there was 37.9% (n=129) patients had delayed the breast cancer journey from symptom discovery until treatment initiation for more than 6 months.

Table 4.20: The proportion of delays in presentation, diagnosis and treatment of breast cancer in Malaysia.

No.	Breast cancer delay	Cutoff points	N	Non-delay n (%)	Delay n (%)
1.	Presentation delay	>3 months	340	221 (65.0)	119 (35.0)
2.	Diagnosis delay	>1 month	340	198 (58.2)	142 (41.8)
3.	Treatment delay	>1 month	340	220 (64.7)	120 (35.3)

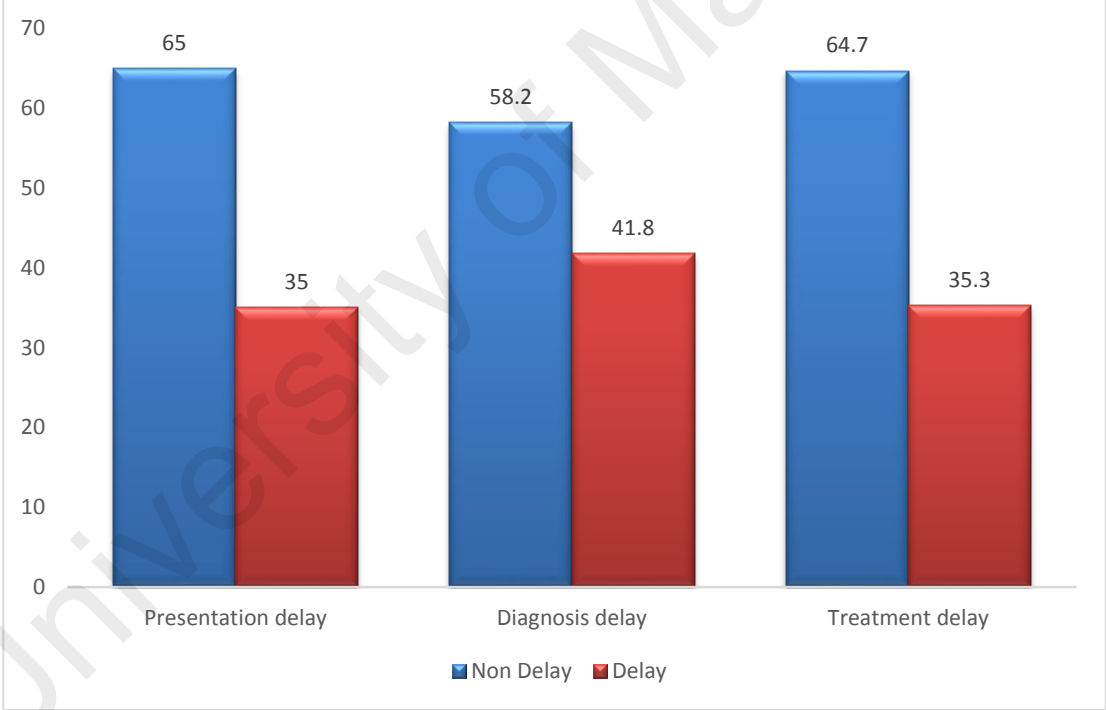


Figure 4.9: The proportion of delays in breast cancer amongst breast cancer patients attending public hospitals in Malaysia

4.5.19 Time taken for presentation according to time categories

Figure 4.10 shows the presentation time among breast cancer patients in Malaysia according to time categories. Delay was further categorized to 0 to 1 month, 1 to 3 months, 3 to 6 months, 6 to 12 months and more than 12 months categories in this section.

Result shows that only 27.9% (n=95) of breast cancer patients presented within 1 month and 65% (n=221) of breast cancer patients presented within 3 month after symptom discovery.

The proportion of presentation delay of more than 3 months was 35% (n=119) and the proportion of presentation delay of more than 6 months was 19.8% (n=67). Approximately, 7.4% (n=25) delayed presentation for more than 1 year.

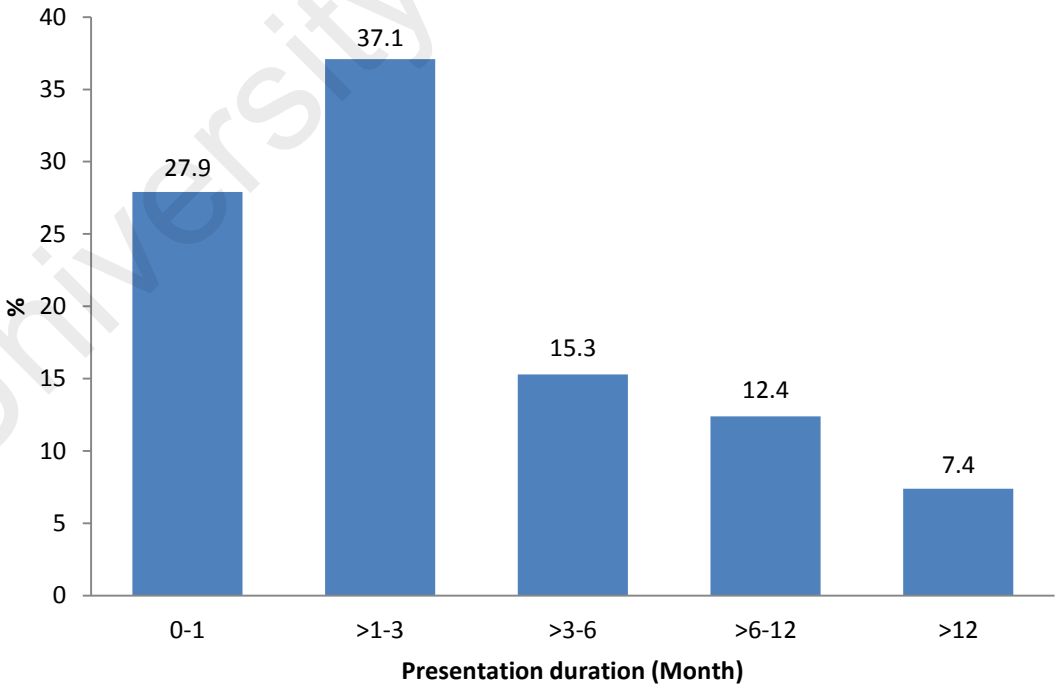


Figure 4.10: Time taken for presentation of breast cancer patients

4.5.20 Time taken for breast cancer diagnosis according to time categories

Figure 4.11 shows the diagnosis time among breast cancer patients in Malaysia according to time categories. This section categories diagnosis time intervals to diagnosis by 0 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days and more than 60 days categories.

Result shows that only 24.7% (n=84) of breast cancer patients were diagnosed within 15 days and 58.2% (n=198) of breast cancer patients were diagnosed within 30 days after presented at primary health care facility.

The proportion of diagnosis delay of more than 30 days was 41.8% (n=142) and the proportion of diagnosis delay of more than 45 days was 26.5% (n=90). Approximately 14.7% (n=50) delayed diagnosis for more than 60 days.

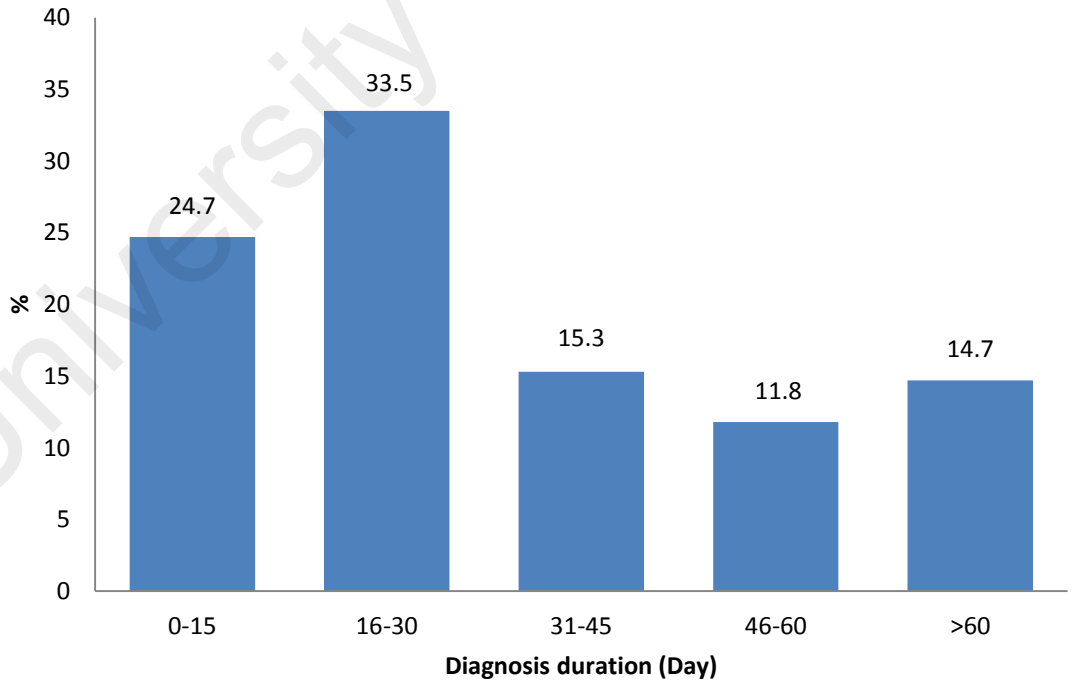


Figure 4.11: Time taken for diagnosis of breast cancer patients

4.5.21 Time taken for breast cancer treatment according to time categories

Figure 4.12 shows the initial treatment time among breast cancer patients in Malaysia according to time categories. This section categories treatment time interval by 0 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days and more than 60 days categories.

Result shows that only 34.1% (n=116) of breast cancer patients were treated within 15 days and 64.7% (n=220) of breast cancer patients were treated within 30 days after diagnosis.

The proportion of treatment delay of more than 30 days was 35.3% (n=120) and the proportion of treatment delay of more than 45 days was 22.1% (n=75). Approximately 10% (n=34) delayed treatment of more than 60 days and 6.5% (n=22) refused for any treatment.

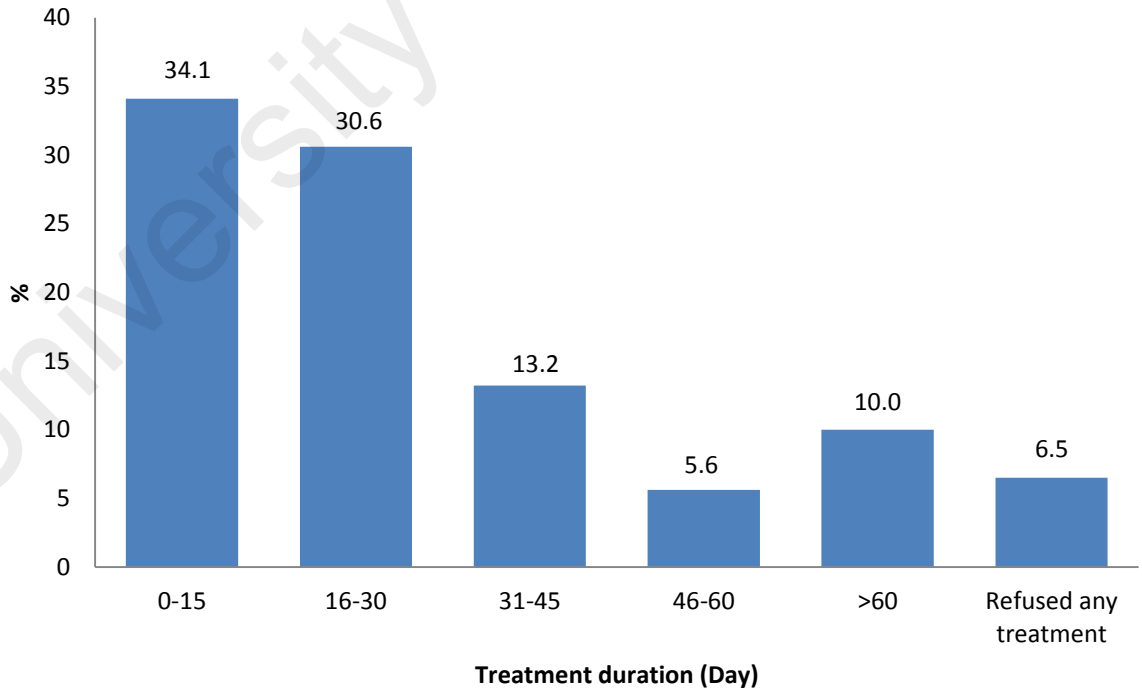


Figure 4.12: Time taken for initial treatment of breast cancer patients

Factors associated with delays in presentation, diagnosis and treatment in breast cancer

4.5.22 Factors associated with delay in presentation among breast cancer patients in Malaysia

Table 4.21 shows the factors associated with delay in presentation among breast cancer patients in Malaysia. Delay in presentation is divided into dichotomous outcomes; non-delay and delay. In this study, the proportion of delay in presentation is 35% with 119 patients delayed their presentation of more than 3 months.

The variables included in the univariate analysis were age group, study locations, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, breast symptom, symptom interpretation, and performed breast self-examination (BSE). All variables were analysed through univariable logistic regression and results were presented as crude odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant. From this analysis, patients in Kelantan, secondary and primary education level and having no family with breast cancer were found to be statistically significant with delay in presentation. The crude odd ratio for patients in Kota Bharu, Kelantan was OR: 4.53 (95% CI: 1.59, 12.84), secondary and primary education level was OR: 1.58 (95% CI: 1.80, 6.14) and having no family with breast cancer was OR: 1.53 (95% CI: 1.83, 4.82).

In multivariate analysis, an adjustment for covariates of study locations, ethnicity, education level, household income, employment status, family history with breast cancer, and performed breast self-examination (BSE) was conducted by using multivariable logistic regression. Findings showed that patients in Kota Bharu, Kelantan was statistically significant with delay in presentation. The odds ratio of delay in presentation

among patients in Kota Bharu, Kelantan was 4.78 times higher (OR 4.78; 95% CI: 1.45, 15.7) than patients in Kuala Lumpur (1). This indicates that patients in Kota Bharu, Kelantan was the independent factors to delay in presentation to primary health care.

The age group, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, breast symptom, symptom interpretation and performed breast self-examination (BSE) were not independently associated with delay in presentation among breast cancer patients in Malaysia.

Table 4.21: Factors associated with delay in presentation amongst breast cancer patients attending public hospitals in Malaysia (N=340)

Variables		Presentation		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay n=221	Delay n=119				
Age group	≤50 years	81 (61.4)	51 (38.6)	1.00	0.263	-	-
	>50 years	140 (67.3)	68 (32.7)	0.77 (0.49, 1.21)			
Study locations	Kuala Lumpur (1)	66 (66.0)	34 (34.0)	1.00	-	1.00	-
	Kuala Lumpur (2)	51 (63.8)	29 (36.3)	1.10 (0.59, 2.04)	0.753	1.24 (0.62, 2.48)	0.537
	Ipoh	39 (81.3)	9 (18.8)	0.44 (0.19, 1.03)	0.059	0.42 (0.17, 1.02)	0.057
	Johor Bahru	31 (62.0)	19 (38.0)	1.19 (0.58, 2.40)	0.629	1.18 (0.53, 2.62)	0.684
	Kota Bharu	6 (30.0)	14 (70.0)	4.53 (1.59, 12.8)	**0.004**	4.78 (1.45, 15.70)	**0.010**
	Kuching	28 (66.7)	14 (33.3)	0.97 (0.45, 2.08)	0.939	1.15 (0.46, 2.85)	0.756
Ethnicity	Chinese	70 (67.3)	34 (32.7)	1.00	-	1.00	-
	Malay	93 (60.4)	61 (39.6)	1.35 (0.80, 2.27)	0.259	1.06 (0.58, 1.95)	0.833
	Indian	39 (72.2)	15 (27.8)	0.79 (0.38, 1.63)	0.527	0.68 (0.30, 1.51)	0.345
	Others	19 (67.9)	9 (32.1)	0.97 (0.39, 2.38)	0.956	0.81 (0.30, 2.21)	0.693
Educational level	Tertiary	36 (73.5)	13 (26.5)	1.00	-	1.00	-
	Secondary & Primary	185 (63.6)	106 (36.4)	1.58 (1.80, 6.14)	**0.038**	1.34 (0.74, 3.63)	0.219
Marital status	Married	171 (66.0)	88 (34.0)	1.00	-	-	-
	Single/Divorced	50 (61.7)	31 (38.2)	1.20 (0.71, 2.02)	0.480		

'Table 4.21, continued'

Variables		Presentation		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay n=221	Delay n=119				
Household income	≤RM3000	163 (66.8)	81 (33.2)	1.00	-	1.00	-
	>RM3000	58 (60.4)	38 (39.6)	1.31 (0.80, 2.14)	0.267	1.23 (0.10, 3.39)	0.122
Employment status	Employed	77 (70.6)	32 (29.4)	1.00	-	1.00	-
	Unemployed	144 (62.3)	87 (37.7)	1.45 (0.89, 2.37)	0.135	1.31 (0.91, 2.87)	0.102
Family with breast cancer	Yes	45 (72.6)	17 (27.4)	1.00	-	1.00	-
	No	176 (63.3)	102 (36.7)	1.53 (1.83, 4.82)	**0.048**	1.28 (0.91, 3.47)	0.090
Breast symptom	With lump	195 (65.0)	105 (35.0)	1.00	-	-	-
	Without lump	26 (65.0)	14 (35.0)	1.00 (0.50, 1.99)	1.000		
Interpret symptom as cancer	Yes	136 (63.3)	79 (36.7)	1.00	-	-	-
	No	85 (68.0)	40 (32.0)	0.81 (0.50, 1.29)	0.377		
Performed BSE	Yes	149 (67.1)	73 (32.9)	1.00	-	1.00	-
	No	72 (61.0)	46 (39.0)	1.30 (0.82, 2.07)	0.262	1.41 (0.82, 2.40)	0.207

BSE=breast self-examination, [a]Univariable Logistic Regression, [b]Multivariable Logistic Regression, Significant value p<0.05

4.5.23 Factors associated with delay in diagnosis among breast cancer patients in Malaysia

Table 4.22 shows the factors associated with delay in diagnosis among breast cancer patients in Malaysia. Delay in diagnosis is divided into dichotomous outcomes; non-delay and delay. In this study, the proportion of delay in diagnosis was 41.8% with 142 patients delayed their diagnosis of more than 1 month.

The variables included in the univariate analysis were age groups, study locations, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, breast symptom, first presentation at primary care facility, diagnosis place, total number of biopsy, and type of biopsy. All variables were analysed through univariable logistic regression and results were presented as crude odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant. From this analysis, patients in Kuala Lumpur (2) and Johor, breast symptom, diagnosis place, number of biopsy and surgical biopsy were found to be statistically significant with delay in diagnosis. The crude odd ratio for patients in Kuala Lumpur (2) and Johor were OR: 3.32 (95% CI: 1.76, 6.28) and OR: 2.92 (95% CI: 1.42, 6.00) respectively. Meanwhile, the crude odd ratio for symptom with breast lump was OR 1.83 (95% CI: 1.54, 3.56), diagnosis place was OR: 2.50 (95% CI: 1.26, 6.93), two or more biopsies was OR: 4.11 (95% CI: 2.53, 6.68) and surgical biopsy was OR: 1.84 (95% CI: 1.04, 3.27).

In multivariate analysis, an adjustment for covariates of study locations, ethnicity, marital status, symptom with lump, first presentation at primary care facility, diagnosis place, total number of biopsy and type of biopsy was conducted by using multivariable logistic regression. Findings showed that patients in Kuala Lumpur (2) and Johor Bahru, symptoms without lump, two or more biopsies and surgical biopsy were statistically significant with delay in diagnosis. The odd ratio for patients in Kuala Lumpur (2) and

Johor Bahru were 3.81 times higher (95% CI: 1.85, 7.85) and 3.13 times higher (95% CI: 1.35, 7.23) than Kuala Lumpur (1) respectively. Meanwhile, the odd ratio for delay in diagnosis among patients without breast lump was 1.98 times higher (OR 1.98; 95% CI: 1.45, 4.12) than those with breast lump, patients underwent two or more biopsies was 3.02 times higher (OR 3.02; 95% CI: 2.42, 6.45) than one biopsy, and patient underwent surgical biopsy was 2.56 times higher (OR 2.56; 95% CI: 1.30, 5.04) than needle biopsy. This indicates that patients in Kuala Lumpur (2) and Johor Bahru, symptoms without lump, two or more biopsies and surgical biopsy were the independent factors to delay in presentation to primary health care.

The age group, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, first presentation at primary care facility and diagnosis place were not independently associated with delay in diagnosis among breast cancer patients in Malaysia.

Table 4.22: Factors associated with delay in diagnosis amongst breast cancer patients attending public hospitals in Malaysia (N=340)

Variables		Diagnosis		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay N=198	Delay N=142				
Age group	≤50 years	78 (59.1)	54 (40.9)	1.00	-	-	-
	>50 years	120 (57.7)	88 (42.3)	1.05 (0.68, 1.64)	0.799		
Study locations	Kuala Lumpur (1)	76 (76.0)	24 (24.0)	1.00	-	1.00	-
	Kuala Lumpur (2)	39 (48.8)	41 (51.3)	3.32 (1.76, 6.28)	**<0.001**	3.81 (1.85, 7.85)	**0.001**
	Ipoh	24 (50.0)	24 (50.0)	1.16 (0.52, 6.56)	0.072	1.53 (0.60, 5.80)	0.101
	Johor Bahru	26 (52.0)	24 (48.0)	2.92 (1.42, 6.00)	**0.004**	3.13 (1.35, 7.23)	**0.008**
	Kota Bharu	9 (45.0)	11 (55.0)	0.87 (0.43, 4.45)	0.208	1.40 (0.34, 4.49)	0.085
	Kuching	24 (57.1)	18 (42.9)	1.37 (0.10, 2.10)	0.127	1.42 (0.95, 6.14)	0.063
Ethnicity	Chinese	63 (60.6)	41 (39.4)	1.00	-	1.00	-
	Malay	85 (55.2)	69 (44.8)	1.24 (0.75, 2.06)	0.391	0.74 (0.41, 1.35)	0.338
	Indian	31 (57.4)	23 (42.6)	1.14 (0.58, 2.22)	0.700	1.17 (0.54, 2.54)	0.689
	Others	19 (67.9)	9 (32.1)	0.72 (0.30, 1.76)	0.482	0.60 (0.20, 1.75)	0.354
Educational level	Tertiary	28 (57.1)	21 (42.9)	1.00	-	-	-
	Secondary & Primary	170 (58.4)	121 (41.6)	0.88 (0.47, 1.64)	0.701		
Marital status	Married	154 (59.5)	105 (40.5)	1.00	-	1.00	-
	Single/Divorced	44 (54.3)	37 (45.7)	1.23 (0.74, 2.03)	0.413	1.37 (0.76, 2.44)	0.287

'Table 4.22, continued'

Variables		Diagnosis		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay N=198	Delay N=142				
Household income	≤RM3000	136 (55.7)	108 (44.3)	1.00	-	-	-
	>RM3000	62 (64.6)	34 (35.4)	0.69 (0.42, 1.12)	0.138		
Employment status	Employed	59 (54.1)	50 (45.9)	1.00	-	-	-
	Unemployed	139 (60.2)	92 (39.8)	0.78 (0.49, 1.23)	0.292		
Family with breast cancer	Yes	31 (50.0)	31 (50.0)	1.00	-	-	-
	No	167 (60.1)	111 (39.9)	0.66 (0.38, 1.15)	0.147		
Breast symptom	With lump	180 (60.0)	120 (40.0)	1.00	-	1.00	-
	Without lump	18 (45.0)	22 (55.0)	1.83 (1.54, 3.56)	**0.044**	1.98 (1.45, 4.12)	**0.028**
First presentation	GP/ KK	170 (58.0)	123 (42.0)	1.00	-	1.00	-
	Hospital	28 (59.6)	19 (40.4)	0.93 (0.50, 1.75)	0.841	0.70 (0.34, 1.44)	0.336
Diagnosis place	Participating hospitals	158 (55.6)	126 (44.4)	1.00	-	1.00	-
	Other hospitals	40 (71.4)	16 (28.6)	2.50 (1.26, 6.93)	**0.031**	0.78 (0.53, 1.65)	0.311
Number of biopsy	1 biopsy	161 (68.8)	73 (31.2)	1.00	-	1.00	-
	≥ 2 biopsies	37 (34.9)	69 (65.1)	4.11 (2.53, 6.68)	**<0.001**	3.02 (2.42, 6.45)	**0.032**
Type of biopsy	Needle	172 (60.8)	111 (39.2)	1.00	-	1.00	-
	Surgical	26 (45.6)	31 (54.4)	1.84 (1.04, 3.27)	**0.036**	2.56 (1.30, 5.04)	**0.006**

GP=general practitioner, [a]Univariable Logistic Regression, [b]Multivariable Logistic Regression, Significant value p<0.05

4.5.24 Factors associated with delay in treatment among breast cancer patients in Malaysia

Table 4.23 shows the factors associated with delay in treatment among breast cancer patients in Malaysia. Delay in treatment is divided into dichotomous outcomes; non-delay and delay. In this study, the proportion of delay in treatment is 35.3% with 142 patients delayed their initial treatment of more than 1 month.

The variables included in the univariate analysis were age groups, study locations, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, diagnosis place, surgical services, oncology services and type of surgery. All variables were analysed through univariable logistic regression and results were presented as crude odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant. From this analysis, patients in Kuala Lumpur (2), Johor Bahru, Kota Bharu, Kuching, Malays and diagnosed at other hospitals were found to be statistically significant with delay in treatment. The crude odd ratio for patients in Kuala Lumpur (2), Johor Bahru, Kota Bahru and Kuching were OR: 3.10 (95% CI: 1.48, 6.49), OR: 4.95 (95% CI: 2.13, 11.5), OR: 6.68 (95% CI: 2.02, 22.06) and OR: 3.88 (95% CI: 1.52, 9.88) respectively. Meanwhile, the crude odd ratio for Malays and diagnosed at other hospitals were OR: 1.75 (95% CI: 1.03, 2.98) and OR: 1.82 (95% CI: 1.02, 3.25) respectively.

In multivariate analysis, an adjustment for covariates of study locations, ethnicity, family history with breast cancer, diagnosis place, surgical services, oncology services, type of surgery was conducted by using multivariable logistic regression. Findings showed that patients in Kuala Lumpur (2), Johor Bahru, Kota Bharu and Kuching, and those diagnosed at other hospitals were statistically significant with delay in treatment. The odds ratio of delay in treatment among patients in Kuala Lumpur (2) was 3.10 times

higher (OR 3.10; 95% CI: 1.48, 6.49), Johor Bahru was 4.95 times higher (OR 4.95; 95% CI: 2.13, 11.5), Kota Bharu was 6.68 times higher (OR 6.68; 95% CI: 2.02, 22.06) and Kuching was 3.88 times higher (OR 3.88; 95% CI: 1.52, 9.88) than patients in Kuala Lumpur (1). Meanwhile, the odds of delay in treatment among those diagnosed at other hospitals was 2.18 times higher (OR 2.18; 95% CI: 1.14, 4.15) than diagnosed at participating hospitals. These indicate that patients in Kuala Lumpur (2), Johor Bharu, Kota Bahru and Kuching, and those diagnosed at other hospitals were the independent factors to delay in treatment.

The age groups, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, surgical services, oncology services and type of surgery were not independently associated with delay in treatment among breast cancer patients in Malaysia.

Table 4.23: Factors associated with delay in treatment amongst breast cancer patients attending public hospitals in Malaysia (N=340)

Variables		Treatment		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay n=217	Delay n=123				
Age group	≤50 years	85 (64.4)	47 (35.6)	1.00	-	-	-
	>50 years	132 (63.5)	76 (36.5)	1.04 (0.66, 1.64)	0.862		
Study locations	Kuala Lumpur (1)	79 (79.0)	21 (21.0)	1.00	-	1.00	-
	Kuala Lumpur (2)	47 (58.8)	33 (41.3)	2.64 (1.37, 5.08)	**0.004**	3.10 (1.48, 6.49)	**0.003**
	Ipoh	34 (70.8)	14 (29.2)	1.54 (0.70, 3.40)	0.276	1.23 (0.75, 3.99)	0.198
	Johor Bahru	25 (50.0)	25 (50.0)	3.76 (1.80, 7.83)	**<0.001**	4.95 (2.13, 11.5)	**<0.001**
	Kota Bharu	8 (40.0)	12 (60.0)	5.64 (2.04, 15.58)	**0.001**	6.68 (2.02, 22.06)	**0.002**
	Kuching	24 (57.1)	18 (42.9)	2.82 (1.29, 6.14)	**0.009**	3.88 (1.52, 9.88)	**0.002**
Ethnicity	Chinese	74 (71.2)	30 (28.8)	1.00	-	1.00	-
	Malay	90 (58.4)	64 (41.6)	1.75 (1.03, 2.98)	**0.038**	1.22 (0.66, 2.25)	0.516
	Indian	34 (63.0)	20 (37.0)	1.45 (0.72, 2.91)	0.295	1.15 (0.88, 4.29)	0.095
	Others	19 (67.9)	9 (32.1)	1.16 (0.47, 2.87)	0.734	0.94 (0.34, 2.61)	0.920
Educational level	Tertiary	32 (65.3)	17 (34.7)	1.00	-	-	-
	Secondary & Primary	185 (51.2)	106 (48.8)	1.00 (0.53, 1.91)	0.980		
Marital status	Married	162 (62.5)	97 (37.5)	1.00	-	-	-
	Single/ Divorced	55 (67.9)	26 (32.1)	0.79 (0.46, 1.34)	0.382		

'Table 4.23, continued'

Variables		Treatment		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Non-delay n=217	Delay n=123				
Household income	≤RM3000	154 (63.1)	90 (36.9)	1.00	-	-	-
	>RM3000	63 (65.6)	33 (34.4)	0.89 (0.54, 1.47)	0.665		
Employment status	Employed	68 (62.4)	41 (37.6)	1.00	-	-	-
	Unemployed	149 (64.5)	82 (35.5)	0.91 (0.56, 1.46)	0.705		
Family history with breast cancer	Yes	33 (53.2)	29 (46.8)	1.00	-	1.00	-
	No	184 (66.2)	94 (33.8)	0.58 (0.33, 1.01)	0.056	0.55 (0.29, 1.02)	0.058
Diagnosis place	Participating hospitals	188 (66.2)	96 (33.8)	1.00	-	1.00	-
	Other hospitals	29 (51.8)	27 (48.2)	1.82 (1.02, 3.25)	**0.042**	2.18 (1.14, 4.15)	**0.017**
Surgical services	Breast surgeon	134 (67.0)	66 (33.0)	1.00	-	1.00	-
	General surgeon	83 (59.3)	57 (40.7)	1.39 (0.89, 2.18)	0.146	1.39 (0.87, 2.23)	0.161
Oncology services	Available	175 (64.3)	97 (35.7)	1.00	-	1.00	-
	Not available	42 (61.8)	26 (38.2)	1.11 (0.64, 1.93)	0.693	0.98 (0.55, 1.75)	0.967
Type of surgery	BCS	116 (54.2)	98 (45.8)	1.00	-	1.00	-
	MAC	40 (34.8)	75 (65.2)	1.22 (0.52, 1.89)	0.349	0.78 (0.43, 1.67)	0.564

BSE=breast self-examination, CAM=complementary and alternative medicine, GP=general practitioner, [a]Univariable Logistic Regression, [b]Multivariable Logistic Regression, Significant value p<0.05

4.5.25 Association between delays in presentation, diagnosis and treatment with stage at diagnosis

Approximately, 17.4%, 37.6%, 33.5% and 11.5% were diagnosed at Stage I, II, III and IV respectively. The stages are then divided into dichotomous outcomes; early stages (Stage I & II) and late stages (Stage III & IV). Among the 340 patients, 187 (55%) were diagnosed at early stages while the remaining 153 (45%) were diagnosed at late stages.

Table 4.24: Stage of cancer among the breast cancer patients

Characteristic	**N**	**n (%)**
Stage		
I	340	59 (17.4)
II		128 (37.6)
III		114 (33.5)
IV		39 (11.5)
Stage		
Early stage	340	187 (55.0)
Late stage		153 (45.0)

4.5.26 Association between delays in presentation and diagnosis with stage of breast cancer

Table 4.25 summarized the association between delay in presentation and diagnosis with stage of breast cancer amongst patients attending public hospitals in Malaysia. A univariate analysis was conducted to look at the association of delays in presentation and diagnosis on stage of cancer.

Results show that the prevalence of late stage is higher in the presentation delay group compared to the non-delay with 53.8% and 40.3% respectively. After univariable logistic regression, presentation delay was found to be significant with late stage cancer (p=0.017). The odds of delay group to be diagnosed at a late stage cancer was 1.72 times higher (OR 1.72; 95% CI: 1.10, 2.70) than the non-delay group.

Similarly, higher prevalence of late stage was also seen in the diagnosis delay group compared to non-delay with 48.6% and 42.4% respectively. However, diagnosis delay was not significant with late stage cancer (p=0.260). This indicates that presentation delay was the associated factor to late stage cancer but not for diagnosis delay.

Table 4.25: The association between delays in presentation and diagnosis with cancer stage

Delays in breast cancer (N=340)	Early stage n (%)	Late stage n (%)	Crude OR (95% CI)	P value
Presentation				
Non-delay	132 (59.7)	89 (40.3)	1.00	-
Delay	55 (46.2)	64 (53.8)	1.72 (1.10, 2.70)	**0.017**
Diagnosis				
Non-delay	114 (57.6)	84 (42.4)	1.00	-
Delay	73 (51.4)	69 (48.6)	1.28 (0.83, 1.97)	0.260

Univariable Logistic Regression, Significant value p<0.05

4.5.27 Association between stage of breast cancer and delay in treatment

Table 4.26 summarized the association between stage of cancer and delay in treatment amongst patients attending public hospitals in Malaysia. A univariate analysis was conducted to look at the association of cancer stage on time to treatment, which is divided into dichotomous outcomes; non-delay and delay.

Results show that the prevalence of delay in treatment was higher in late stage group compared to the early stage with 38.6% and 34.2% respectively. However, after univariable logistic regression, stage of cancer was not significant with delay in treatment (p=0.408). This indicates that stage of cancer was not an associated factor to treatment delay.

Table 4.26: The association between stage of cancer and delay in treatment

Delays in breast cancer (N=340)	Treatment		Crude OR (95% CI)	P value
	Non delay n (%)	Delay n (%)		
Cancer stage				
Early stage	123 (65.8)	64 (34.2)	1.00	-
Late stage	94 (61.4)	59 (38.6)	1.20 (0.77, 1.88)	0.408

Univariable Logistic Regression, Significant value p<0.05

Factors associated with non-adherence to treatments among the breast cancer patients in Malaysia

4.5.28 Factors associated with non-adherence to surgery among breast cancer patients in Malaysia

Table 4.27 shows the factors associated with non-adherence to surgery among breast cancer patients in Malaysia. Adherence to surgery is divided into dichotomous outcomes; adherence and non-adherence. In this study, the proportion of non-adherence to surgery is 14% with 46 patients not adhering to their surgery.

The variables included in the analysis are age group, study locations, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, symptom included breast lump, diagnosis place, stage at diagnosis, type of surgery, surgical type and oncology services. All variables were analysed through univariate and multivariate analysis with significant value of less than 0.05.

In univariate analysis, patients in Kuala Lumpur (2), Johor Bahru and Kota Bharu, Malays, secondary education level, late stage diagnosis and eligible for mastectomy (MAC) were found to be statistically significant with non-adherence to surgery. The crude odd ratio for patients in Kuala Lumpur (2), Johor and Kelantan were OR: 3.31 (95% CI: 1.21, 9.09), OR: 9.54 (95% CI: 3.42, 26.61) and OR: 6.50 (95% CI: 1.83, 23.01) respectively. Meanwhile, the crude odd ratio for Malays, secondary education level, late stage at diagnosis and recommended for MAC were OR: 4.10 (95% CI: 1.64, 10.26), OR: 9.58 (95% CI: 1.28, 71.39), OR: 2.52 (95% CI: 1.32, 4.81) and OR: 5.55 (95% CI: 1.67, 18.40) respectively.

In multivariate analysis, an adjustment for all covariates was conducted by using multivariable logistic regression. Results found that patients in Kuala Lumpur (2), Johor

Bahru, and Kota Bharu, and those recommended for mastectomy (MAC) were statistically significant with non-adherence to surgery.

The odds of non-adherence to surgery among patients in Kuala Lumpur (2) was 3.41 times higher (OR 3.41; 95% CI: 1.00, 11.60), Johor Bahru was 8.38 times higher (OR 8.38; 95% CI: 2.38, 29.51) and Kota Bharu was 6.32 times higher (OR 6.32; 95% CI: 1.20, 33.23) than women in Kuala Lumpur (1). Meanwhile, the odds of non-adherence to surgery among those recommended for MAC was 5.66 times higher (OR 5.66; 95% CI: 1.52, 21.03) than BCS.

These indicates that patients in Kuala Lumpur (2), Johor Bahru, Kota Bharu and recommended for MAC were the independent factors to non-adherence to surgery. Patients in Kuala Lumpur (1), Ipoh and Kuching, age group, education status, marital status, household income, employment status, family history with breast cancer, symptom included breast lump, stage at diagnosis, type of surgical services and oncology services, are not independently associated with non-adherence to surgery among breast cancer patients in Malaysia.

Table 4.27: Factors associated with non-adherence to surgery amongst breast cancer patients attending public hospitals in Malaysia (N=329)

Variables		Surgery		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Adherence n=283 (86%)	Non-adherence n=46 (14%)				
Age group	≤50 years	109 (85.2)	19 (14.8)	1.00	-	1.00	-
	>50 years	174 (86.6)	27 (13.4)	0.89 (0.47, 1.67)	0.719	0.96 (0.41, 2.23)	0.927
Study locations	Kuala Lumpur (1)	91 (93.8)	6 (6.2)	1.00	-	1.00	-
	Kuala Lumpur (2)	64 (82.1)	14 (17.9)	3.31 (1.21, 9.09)	**0.020**	3.41 (1.00, 11.60)	**0.050**
	Ipoh	48 (100)	0 (0)	0.01 (0.11, 4.32)	0.997	0.01 (0.00, 3.41)	0.997
	Johor Bahru	27 (61.4)	17 (38.6)	9.54 (3.42, 26.61)	**<0.001**	8.38 (2.38, 29.51)	**0.001**
	Kota Bharu	14 (70.0)	6 (30.0)	6.50 (1.83, 23.01)	**0.004**	6.32 (1.20, 33.23)	**0.029**
	Kuching	39 (92.9)	3 (7.1)	1.16 (0.27, 4.90)	0.833	1.81 (0.33, 9.81)	0.491
Ethnicity	Chinese	93 (93.9)	6 (6.1)	1.00	-	1.00	-
	Malay	117 (79.1)	31 (20.9)	4.10 (1.64, 10.26)	**0.002**	4.11 (0.72, 6.22)	0.173
	Indian	47 (87.0)	7 (13.0)	2.30 (0.73, 7.25)	0.152	2.67 (0.12, 19.38)	0.134
	Others	26 (92.9)	2 (7.1)	1.19 (0.22, 6.26)	0.835	1.26 (0.20, 7.94)	0.806
Educational level	Tertiary	47 (97.9)	1 (2.1)	1.00	-	1.00	-
	Secondary	206 (83.1)	42 (16.9)	9.58 (1.28, 71.39)	**0.027**	2.06 (0.40, 103.42)	0.123
	Primary	30 (90.9)	3 (9.1)	4.70 (0.46, 47.30)	0.189	4.23 (0.33, 54.31)	0.268
Marital status	Married	215 (86.0)	35 (14.0)	1.00	-	1.00	-
	Single/Divorced	68 (86.1)	11 (13.9)	0.99 (0.47, 2.06)	0.986	1.29 (0.50, 3.28)	0.593

'Table 4.27, continued'

Variables		Surgery		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Adherence n=283 (86%)	Adherence n=283 (86%)				
Employment status	Employed	92 (87.6)	13 (12.4)	1.00	-	1.00	-
	Unemployed	191 (85.3)	33 (14.7)	1.22 (0.61, 2.43)	0.567	1.16 (0.47, 2.85)	0.746
Family history with breast cancer	Yes	50 (86.2)	8 (13.8)	1.00	-	1.00	-
	No	233 (86.0)	38 (14.0)	1.01 (0.44, 2.31)	0.964	0.97 (0.34, 2.75)	0.957
Breast Symptom	With lump	252 (86.9)	38 (13.1)	1.00	-	1.00	-
	Without lump	31 (79.5)	8 (20.5)	1.71 (0.73, 3.99)	0.215	1.15 (0.38, 3.52)	0.797
Diagnosis place	Studied hospitals	241 (87.6)	34 (12.4)	1.00	-	1.00	-
	Other hospitals	42 (77.8)	12 (22.2)	2.02 (0.97, 4.22)	0.060	3.10 (0.19, 8.05)	0.120
Stage at diagnosis	Early stage	169 (90.9)	17 (9.1)	1.00	-	1.00	-
	Late stage	114 (79.7)	29 (20.3)	2.52 (1.32, 4.81)	**0.005**	1.61 (0.73, 3.55)	0.237
Type of surgery	BCS	79 (96.3)	3 (3.7)	1.00	-	1.00	-
	MAC	204 (82.6)	43 (17.4)	5.55 (1.67, 18.40)	**0.005**	5.66 (1.52, 21.03)	**0.010**
Surgical services	Breast surgeon	169 (86.7)	26 (13.3)	1.00	-	1.00	-
	General surgeon	114 (85.1)	20 (14.9)	1.14 (0.60, 2.14)	0.683	1.34 (0.69, 2.58)	0.380
Oncology services	Available	221 (84.7)	40 (15.3)	1.00	-	1.00	-
	Not available	62 (91.2)	6 (8.8)	0.53 (0.21, 1.31)	0.174	0.47 (0.18, 1.22)	0.123

[a]Univariable Logistic Regression, [b]Multivariable Logistic Regression, Significant value p<0.05

4.5.29 Factors associated with non-adherence to oncology therapy among breast cancer patients in Malaysia

Factors associated with non-adherence to each treatment modalities (e.g. chemotherapy, radiotherapy, hormonal therapy) were done. However, no factors were found to be associated with non-adherence to each treatment. Therefore, these 3 treatment modalities were then combined and analyzed as oncology therapy.

Table 4.28 shows the factors associated with non-adherence to oncology therapy among breast cancer patients in Malaysia. Adherence to oncology therapy is divided into dichotomous outcomes; adherence and non-adherence. Patients who did not adhere to one or more treatment modalities were categorized as non-adherent. From the total of 340 patients, 302 were recommended for oncology therapy. The proportion of non-adherence to oncology therapy was 74.2% with 224 patients not adhering to at least one of the oncology therapy; (e.g. chemotherapy, radiotherapy, hormonal therapy).

The variables included in the analysis were age groups, study location, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, symptom included breast lump, diagnosis place, stage at diagnosis, and oncology services. All variables were analysed through univariate and multivariate analysis with significant value of less than 0.05.

In univariate analysis, patients in Ipoh, Perak, symptom excluding breast lump and hospitals without oncology services were found to be statistically significant with non-adherence to oncology therapy. The crude odd ratio for patients in Ipoh was OR: 1.38 (95% CI: 1.17, 1.82), symptom excluding breast lump was OR: 1.47 (95% CI: 1.22, 1.98) and hospitals without oncology services was OR: 1.50 (95% CI: 1.27, 1.91).

In multivariate analysis, an adjustment for all covariates was conducted by using multivariable logistic regression. Result found that only study location was significant. Patients in Ipoh were an independent factor to non-adherence to oncology therapy. The odds of non-adherence to oncology therapy among patients in Ipoh was 1.42 times higher (OR 1.42; 95% CI: 1.18, 1.97) than patients in Kuala Lumpur (1).

Age groups, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, symptom included breast lump, diagnosis place, stage at diagnosis and oncology services are not independently associated with non-adherence to oncology therapy among breast cancer patients in Malaysia.

Table 4.28: Factors associated with non-adherence to oncology therapy amongst breast cancer patients attending public hospitals in Malaysia (N=302)

Variables		Oncology therapy		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Adherence n=78 (25.8%)	Non-adherence n=224 (74.2%)				
Age group	≤50 years	34 (27.6)	89 (72.4)	1.00	-	1.00	-
	>50 years	44 (24.6)	135 (75.4)	1.17 (0.69, 1.97)	0.551	1.24 (0.67, 2.30)	0.481
Study locations	Kuala Lumpur (1)	22 (23.9)	70 (76.1)	1.00	-	1.00	-
	Kuala Lumpur (2)	17 (27.4)	45 (72.6)	0.83 (0.39, 1.73)	0.624	0.94 (0.41, 2.15)	0.894
	Ipoh	19 (45.2)	23 (54.8)	1.38 (1.17, 1.82)	**0.014**	1.42 (1.18, 1.97)	**0.043**
	Johor Bahru	9 (20.5)	35 (79.5)	1.22 (0.50, 2.93)	0.653	1.54 (0.58, 4.10)	0.383
	Kota Bharu	4 (20.0)	16 (80.0)	1.25 (0.38, 4.15)	0.708	1.76 (0.45, 6.84)	0.412
	Kuching	7 (16.7)	35 (83.3)	1.57 (0.61, 4.03)	0.347	1.88 (0.62, 5.69)	0.263
Ethnicity	Chinese	21 (23.3)	69 (76.7)	1.00	-	1.00	-
	Malay	42 (29.6)	100 (70.4)	0.72 (0.39, 1.33)	0.298	0.67 (0.34, 1.35)	0.272
	Indian	10 (22.7)	34 (77.3)	1.03 (0.43, 2.44)	0.938	1.16 (0.46, 2.93)	0.749
	Others	5 (19.2)	21 (80.8)	1.27 (0.42, 3.80)	0.659	1.06 (0.32, 3.47)	0.923
Educational level	Tertiary	10 (22.2)	35 (77.8)	1.00	-	1.00	-
	Secondary	59 (25.9)	169 (74.1)	0.81 (0.38, 1.75)	0.607	0.78 (0.32, 1.87)	0.586
	Primary	9 (31.0)	20 (69.0)	0.63 (0.22, 1.82)	0.399	0.40 (0.11, 1.43)	0.161

'Table 4.28, continued'

Variables		Oncology therapy		Crude	P	Adjusted	P
		Adherence n=78 (25.8%)	Non-adherence n=224 (74.2%)	Odd Ratio (95% CI)	value[a]	Odd Ratio (95% CI)	value[b]
Marital status	Married	62 (26.8)	169 (73.2)	1.00	-	1.00	-
	Single/Divorced	16 (22.5)	55 (77.5)	1.26 (0.67, 2.36)	0.469	1.19 (0.60, 2.35)	0.609
Household income	≤RM3000	51 (23.7)	164 (76.3)	1.00	-	1.00	-
	>RM3000	27 (31.0)	60 (69.0)	0.69 (0.39, 1.20)	0.190	0.67 (0.36, 1.27)	0.227
Employment status	Employed	27 (27.8)	70 (72.2)	1.00	-	1.00	-
	Unemployed	51 (24.9)	154 (75.1)	1.16 (0.67, 2.00)	0.584	1.06 (0.55, 2.01)	0.855
Family history with breast cancer	Yes	13 (25.0)	39 (75.0)	1.00	-	1.00	-
	No	65 (26.0)	185 (74.0)	0.94 (0.47, 1.88)	0.881	1.03 (0.49, 2.18)	0.925
Symptom included breast lump	Yes	64 (24.0)	203 (76.0)	1.00	-	1.00	-
	No	14 (40.0)	21 (60.0)	1.47 (1.22, 1.98)	**0.045**	0.50 (0.22, 1.09)	0.084
Diagnosis place	Studied hospitals	64 (25.7)	185 (74.3)	1.00	-	1.00	-
	Other hospitals	14 (26.4)	39 (73.6)	0.96 (0.49, 1.89)	0.914	0.93 (0.45, 1.91)	0.847
Stage at diagnosis	Early stage	41 (25.6)	119 (74.4)	1.00	-	1.00	-
	Late stage	37 (26.1)	105 (73.9)	0.97 (0.58, 1.63)	0.932	1.06 (0.56, 1.78)	0.983

'Table 4.28, continued'

Variables		Oncology therapy		Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
		Adherence n=78 (25.8%)	Non-adherence n=224 (74.2%)				
Oncology services	Available	55 (22.9)	185 (77.1)	1.00	-	1.00	-
	Not available	23 (37.1)	39 (62.9)	1.50 (1.27, 1.91)	**0.024**	1.45 (0.77, 2.56)	0.675

CAM=complementary and alternative medicine
[a]Univariable Logistic Regression, [b]Multivariable Logistic Regression
Significant value p<0.05

4.5.30 Result summary

In summary, the median time to presentation, diagnosis and treatment in this study were 2.4 months, 26 days and 21 days respectively, and median time to referral, biopsy, report and disclosure were 8 days, 0 day, 7 days and 4 days respectively. Meanwhile, the median time to surgery, chemotherapy, radiotherapy and hormonal therapy after diagnosis were 22 days, 57 days, 190 days and 212 days respectively.

There were high proportions of delays in presentation, diagnosis and treatment with 35%, 41.8%, and 35.3% respectively among patients attending public hospitals in Malaysia. The proportions of non-adherence to surgery was low which was 14% but was high for chemotherapy, radiotherapy and hormonal therapy with 30%, 33.3% and 36.3% respectively.

Factors associated with presentation delay were patients in Kelantan and CAM users. Factors associated with diagnosis delay were CAM users, symptoms without lump, underwent two or more biopsies and surgical biopsy. Factors associated with treatment delay were patients in Kuala Lumpur (2), Johor, Kelantan and Sarawak, and those diagnosed at other hospitals. Factors associated with non-adherence to surgery was patients in Kuala Lumpur (2), Johor and Kelantan, and MAC surgery, while factors associated with non-adherence to oncology therapy was patients in Perak.

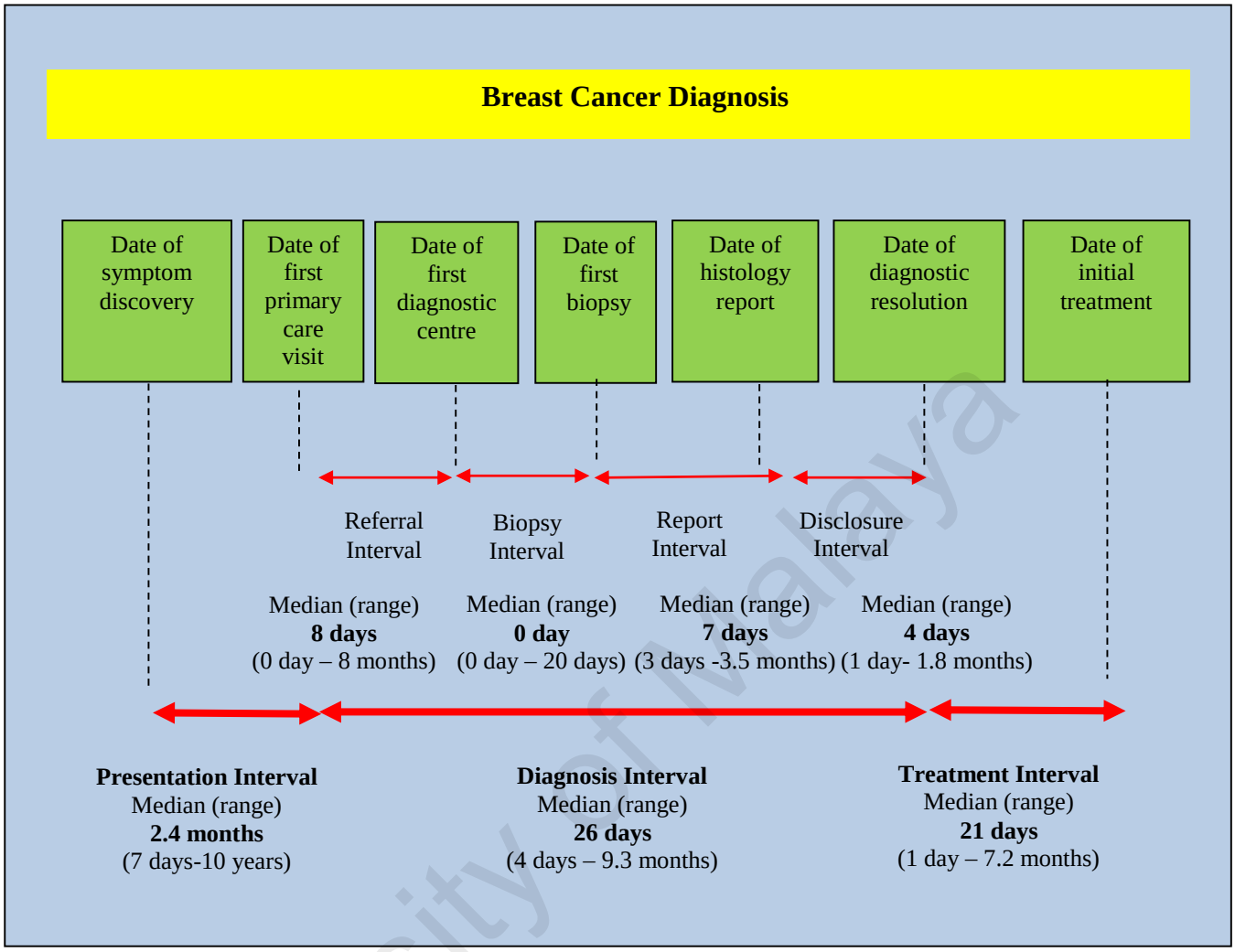


Figure 4.13: The median time intervals of breast cancer journey in Malaysia

4.6 Discussion

The discussion was divided into 5 parts. (1) characteristics of the breast cancer patients, (2) Presentation delay; which consists of presentation details, the time intervals, proportions of presentation delay and factors associated with presentation delays, (3) Diagnosis delay; which consists of diagnosis details, the time intervals, proportions of diagnosis delay and factors associated with diagnosis delays, (4) Treatment delay; which consists of treatment details, the time intervals, proportions of treatment delay and factors associated with treatment delays, (5) The non-adherence to breast cancer treatment; which consists of the factors associated with non-adherence to surgery and oncology therapy.

4.6.1 Characteristics of the breast cancer patients

Of the 340 breast cancer patients seen in this study, 61.2% are above the age of 50 with median of 53 years. These findings are similar to other studies in Malaysia as reported in the national cancer registry (NCR) of Malaysia which showed a peak at the 50-59 age groups (Zainal Ariffin & Nor Saleha, 2011), local studies (Ghazali et al., 2013; Lim et al., 2014; Yip et al., 2011; Cheng et al., 2015; Leong et al., 2007) and other Asian countries (Chen, Kung, Huang, Wang, & Tsai, 2015; Poum et al., 2014; Sy et al., 2015; Yau et al., 2010). However, it is slightly younger as compared to Indonesian and Korean patients (Ng et al., 2011; You et al., 2015). In comparison with Western countries where the median breast cancer age is 60 years (American Cancer Society, 2015), Malaysian women present with breast cancer at a much earlier age due to the cohort effect (Yip and Ng, 1996) where older women in Malaysia has not been exposed to similar risk factors compared to younger women. Besides, it also could be explained due to the population structure where majority of the population in Malaysia is young (Yip et al., 2006). Furthermore, 19.8 million people out of 28.3 million (69.9%) in Malaysia were under 40 years of age (Department of Statistic Malaysia, 2012).

Comparatively, the median age among Malays in this study was 48 years which is relatively younger than other ethnicity in Malaysia. The difference in the population structure between the Malays and other ethnicity is due to the higher fertility rate and younger age groups among Malay as seen in other study (Yip et al., 2006). Between locations, patients from Kelantan in this study were diagnosed at a younger age with a median of 46 years compared to 50-53 years in the other study locations. The reasons for younger age at diagnosis amongst Malays and Kelantanese was not investigated in this study but we believe that this could be related to the genetic susceptibility. Therefore, more detailed studies should be conducted to determine why Malay women commonly are inflicted with breast cancer at a young age compared to other ethnicity and locations in Malaysia.

Majority of the breast cancer patients in this study was Malays, similarly seen in other studies conducted at public hospitals in Malaysia (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011). In contrast, the national cancer registry had reported that Chinese had the highest incidence of breast cancer in Malaysia (Zainal Ariffin & Nor Saleha, 2011). The high proportion of Malay patients in this study could be attributed by the trend in which Chinese patients prefer seeking treatment at private hospitals compared to public hospitals (Institute for Public Health, 2015). In addition, the Median Monthly Gross Household Income by Ethnic Group, Strata and State, Malaysia, 1970-2014 (EPU, 2016) which was conducted in Peninsular Malaysia had reported that the Malays has the lowest median household income compared to other ethnicities in Malaysia, which may explain this findings. However, in West Malaysia, Chinese was the highest group in Sarawak as seen in another study in Sabah (Leong et al., 2007). This suggests that the distribution of public hospital services utilization by ethnicity differs between Peninsular and West Malaysia.

Majority of the breast cancer patients in this study were married and most of them had secondary school education. The median monthly household income was RM2, 803 (~USD 670) per month. Out of all patients, 67% had income less than the Malaysia median monthly household income of RM4,585 (~USD 1,097.55) and 48% had income less than the Malaysia poverty level income of RM 3,000 (~USD 677.89) (Department of Statistics Malaysia, 2015). The reasons for lower social class and lower monthly household income among majority of patients in this study would be related to these groups utilizing subsidised treatment expenses in the public sector.

Public health services in Malaysia charge a minimal fee and do not require private health insurance for the services. All Malaysian citizens could freely access the affordable healthcare services without compromise as the government provides almost free and highly subsidized healthcare services. However, the socio-economic disparity among the patients leads to the imbalance of ethnicities in utilizing public health services in Malaysia. Further studies should be conducted to understand the accessibility and utilization of public cancer services in Malaysia.

4.6.2 Presentation delay

4.6.2.1 Presentation details amongst patients attending public hospitals in Malaysia

All patients in this study presented with symptomatic breast cancer and none of them were detected through mammographic screening. The practice of mammogram screening among Malaysian women has been reported to be low with only 6.8-25.5% of women in

Malaysia have mammogram screening (Al-Naggar & Bobryshev, 2012; Dahlui et al., 2013; Dahlui et al., 2012). Despite being established as the primary imaging screening method for breast cancer and availability of subsidized screening (Ministry of Health Malaysia, 2010), the proportion of mammogram utilization in Malaysia is still low (Yip et al., 2006). This could be explained by the RM100 subsidised mammograms coupons made only available to high risk women from 40 years of age with household income below RM5000 (LPPKN, 2014). Population based screening is not offered in Malaysia due to high cost and limited expertise in the health system (Norsa'adah et al., 2011). Lack of knowledge, not knowing where to go for the test and fear of diagnosis amongst patients were the barriers for opportunistic mammogram screening in Malaysia (Al-Naggar & Bobryshev, 2012).

The uptake of breast self-examination (BSE) in the same study is 65.3% similar to 56-60% as seen in other studies in Malaysia (Dahlui et al., 2013; Dahlui et al., 2012; Ghazali et al., 2013). Based on the clinical practice guideline on management of breast cancer (CPG), breast self-examination (BSE) and clinical breast examination (CBE) were recommended for raising awareness instead as a screening method (Ministry of Health Malaysia, 2010), due to ineffectiveness in reducing breast cancer mortality (Kosters et al., 2008; Thistlethwaite et al., 2007). However, a recent study in India showed that CBE reduce cancer stage (Sankaranarayanan et al., 2011). Thus, an update to this guideline is needed to consider recommendation for CBE as a screening method in Malaysia.

The commonest presenting symptom among patients in this study was presenting with breast lump (88%), as seen in other studies in Malaysia where 80-95% lump in the breast was the commonest presentation and was felt by the patients herself (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011; Taib et al., 2011; Yip et al., 2006). Similarly, a study conducted in 12 middle and low income countries also reported that

breast lump is the most common symptom detected through self-examination by breast cancer patients (Jassem et al., 2013). This illustrates that breast lump as the commonest symptom among breast cancer patients in developing countries. Although breast lump is the commonest symptom, all women should be educated and well-informed that breast cancer can also present with symptoms other than lump such as pain, dimpling, swelling or nipple discharge (Norsa'adah et al., 2011). This is important as knowledge regarding the variation of symptoms in breast cancer enables patients to interpret the symptoms correctly and influences their assessment of symptoms as well as their decision to seek medical attention.

In this study, 36.8% of patients interpreted their symptom as non-cancerous, this suggests that the symptom interpretation among the Malaysian women was poor. Perception of the seriousness of a symptom is dependent upon the first symptom and how fast the symptom changes and escalates (Norsa'adah et al., 2011) due to the hetereogenity of cancer biology and could be worse for those with asymptomatic or painless lump. Knowledge about breast cancer symptoms is important for patients' decision in seeking medical help (Bish et al., 2005; Burgess et al., 1998). This finding illustrates that patients' interpretation on their symptoms as a sign of cancer had an important influence of whether they sought medical help immediately. Many studies have shown that symptom recognition remains an important global public health issue (Jones et al., 2014; Macleod et al., 2009; Quaife et al., 2014; Sharma et al., 2013; Taib et al., 2011), highlighting the need to educate women on early signs and symptom of breast cancer and hence promoting early detection.

Generally, patients will present to primary health care facilities to seek help after recognising symptoms. From this study, majority (86.2%) of patients went to public or private clinics for their first primary health care visit and referred to the diagnostic centre

for further investigations. The health systems encourage primary healthcare services, either public or private clinic to reduce burden or excess of demand for services in public hospitals. Public clinics in Malaysia are heavily subsidized and may be provided free of charge or for a small fee, while private clinics are easily accessible and provided at an affordable cost may contribute to this finding. Besides, some 97.7% of residents surveyed in the Community Residency Program (CRP) live within 5km radius from the nearest clinic (CRP Report, 2009), suggests that primary health care facilities in Malaysia are easily accessible.

4.6.2.2 Time interval between symptoms discovery and presentation to a primary health care amongst patients attending public hospitals in Malaysia

The median time of presentation to primary health care was 2.4 months which was the longest interval than time to diagnosis and treatment in this study. In comparison to other studies in Malaysia, time to presentation in this study was consistent with studies in Kuala Lumpur (Taib et al., 2007; Yip et al., 2006; Ghazali et al., 2013), but shorter than studies in East Coast Malaysia and Johor (Cheng et al., 2015; Norsa'adah et al., 2011;). The variations of these data supported our findings that time in presentation for seeking medical care among breast cancer patients varies between institutions or the study locations in Malaysia.

Although the presentation interval in our study was better than 3.8-12 months of presentation interval in other Asia countries, it was longer than 12 days in Thailand (Poum et al., 2014) and 14-33 days in US and Poland (Jassem et al., 2013; Ruddy et al., 2014), illustrating a much longer time in seeking help process after discovering breast cancer symptoms among patients in Malaysia.

4.6.2.3 The proportions of delays in presentation amongst patients attending public hospitals in Malaysia.

The proportion of presentation delay in this study was 35%. It was consistent with 33-59% than other studies in Malaysia (Cheng et al., 2015; Ghazali et al., 2013; Norsa'adah et al., 2011). However, in comparison to other Asia and developed countries, our figure was much higher than 17-25% from studies in Thailand, Hong Kong and Iran (Montazeri et al., 2003; Poum et al., 2014; Yau et al., 2010) and 8.2-19% from studies in US and UK (Burgess et al., 1998; Quaife et al., 2014; Ruddy et al., 2014). This suggests that breast cancer patients in Malaysia were generally present late and delayed seeking medical help, thus illustrates that presentation delay amongst the breast cancer patients was high and is a serious problem in Malaysia.

4.6.2.4 Factors associated with presentation delay

This study explores the delay in presentation among breast cancer patients by trying to determine the factors associated with delay presenting to primary health care after discovering the breast cancer symptoms. The discussion throughout this section will be guided by exploring the barriers to health seeking behaviour among breast cancer patients in Malaysia.

Presentation delay varied by location and patients in Kelantan was an independent factor for presentation delay in this study. Although this finding was adjusted by socio-demographic factors, we believe that the patient interval prolongation is primarily influenced by the patients' help-seeking behavior which varies according to the local culture and social context. Socio-cultural was found to effects on health decision when there is lack of self-management, lack of family support especially husband and too reliance on family decision (Taib et al., 2011; Norsa'adah et al., 2012; Taib et al., 2013; Yu et al., 2015). This finding was supported by a qualitative study conducted in Kelantan

which reported that the elements for health seeking trajectories were based on the symptoms experience, symptoms perception, symptoms interpretation, social network and quality of health services (Yusoff et al., 2011). Moreover, the East-Coast of Malaysia is more rural and less developed than the West Coast of Peninsular Malaysia (Norsa'adah et al., 2012), supports the findings on culture of Asian women especially for those who live in suburban communities and rural society areas are more private in their perception of their bodies and less receptive to revealing their private parts even to the health care providers (Harirchi et al., 2005; Poum et al., 2014). The perceptions of pain and notions of modesty are subjective and often affected by social perceptions (Chang et al., 2011). Study findings suggest that the socio-culture and socio-economic norms play a huge role in the late presentation among Kelantanese patients, proved that the help-seeking in the health issues may differ in the populations and societies studied.

Our study found that delay in presentation was significantly associated with late stage breast cancer disease as seen in other studies (Ali et al., 2008; Cheng et al., 2015; Ghazali et al., 2013; Montazeri et al., 2003). Studies have reported that Malaysian patients preferred to monitor the symptom progression before making the decision to seek help (Norsa'adah et al., 2012). Unfortunately, most symptoms would have worsened and would eventually come with late stage of disease (Arndt et al., 2002; Taib et al., 2007). In contrast, it is also reported that patients with aggressive types of cancer are prone to present earlier due to high index of cancer suspicion (Norsa'adah et al., 2011). Nevertheless, our study found that those who delayed presentation beyond 3 months was at a higher risk of being diagnosed at late stage disease than those who present early as seen in another study (Cheng et al., 2015). This illustrates that breast cancer patients attending public hospitals in Malaysia are generally waiting much longer before presenting for medical consultation which eventually progresses to a late stage cancer. Although the factors for late stage diagnosis are not specifically studied in this study,

other studies showed that disease stage are influenced by ethnicity, education level, socio-economic status and access to treatment centres (Cheng et al., 2015; Leong et al., 2007; Rajan et al., 2011) and Malays was at higher risk to be diagnosed with larger tumours and advanced stages than other ethnicities (Nirmala Bhoo-Pathy et al., 2012).

Sociodemographic factors such as age group, ethnicity, financial status and marital status do not emerge as significant factors for presentation delay as seen in other studies (Norsa'adah et al., 2011; Alhurishi et al., 2011; Nosarti, 2000; Meechan, 2003). However, some studies shows conflicting results. Older age was found to be the risk factor for presentation delay (Ramirez et al, 1999; Harirchi et al., 2005; Macleod et al., 2009) and conversely some studies reported that delay was longer among younger patients (Ibrahim & Oludara, 2012; Taib et al., 2008; Ruddy et al., 2014; Sainsbury et al., 1999; Samphao et al., 2009). Meanwhile, a local study conducted in Kuala Lumpur reported that Chinese patients were at a higher risk to delay presentation due to higher risk of complementary and alternative medicine (CAM) use (Ghazali et al., 2013). Moreover, it is also possible that financial measurement may have been underestimated since patients may be reluctant to report detailed financial commitments and lack of variation in the sample distribution might be the reasons for insignificance of financial status for presentation delay (Ghazali et al., 2013). Besides that, several studies reported that divorced or widowed patients are associated with delay due to lack of moral support and need help from other quarters to improve their health seeking behavior for obtaining optimum healthcare (Ali et al., 2008; Ghazali et al., 2013; Montazeri et al., 2003) whereas another study reported that delay is associated amongst married patients due to them being actively responsible in taking care of their family (Harirchi et al., 2005).

Family history of breast cancer was not associated with delay in presentation in this study. Having a history of breast cancer does not increase a patient's suspicion

towards breast symptoms (Ghazali et al., 2013). There was no any differences in size, stage and symptoms duration among Malaysian patients with or without a family history of breast cancer and only 10.7% of tumors in patients with family history detected on screening (Yip et al., 2008). This indicates that knowledge of the genetic susceptibility to breast cancer among Malaysian patients with a family history of the disease is still lacking. Genetic testing and knowledge of the BRCA 1 and BRCA 2 genes although have been introduced, the accessibility is still very rudimentary in Malaysia (Nakamura et al., 2016). Stratification of risk is essential for detecting women at high-risk of breast cancer in order to promote early detection of high risk individuals for targeted screening, hence improving breast cancer survival in this group of women.

Accessibility to health care in Malaysia may not be a factor of delayed presentation of breast cancer patients. A Community Residency Program (CRP) survey of medical students in University Malaya reported that 97.7% of residents live within 5km radius from the nearest clinic and 20km radius from the nearest hospital in Malaysia (CRP Report, 2009). This is supported by another study in Taiwan, reported that accessibility to the health care is not a factor for the delay in presentation of breast cancer (Shieh et al., 2014). In comparison to medical insurance policy in Western countries, treatment in Malaysia is heavily subsidized, where patients pay a small fee for public medical care services (Norsa'adah et al., 2012). In addition, a study on performance of breast cancer care services in Malaysia reported that 75-80% of breast cancer patients could access timely treatments (Lim et al., 2014; Yip et al., 2011). However, a qualitative study has shown that delayed presentation can be complex. Patients delay presentation as they felt public hospitals cannot provide a good care as compared to a high-priced private care (Taib et al., 2014). Since public health system in Malaysia has fulfilled most of the accessibility components and patients' acceptability is subjective, it is suggested that

access to health care may not be the main factor in seeking medical care and presentation delay at public hospitals in Malaysia.

Even though public health care facilities were easily accessible, there was a lack of community educational programs in Malaysia (Taib et al., 2014). Patients may not know where to go and how to utilize the available health services. Therefore, improving the breast health literacy at the primary health care level, concentrating on knowledge of how to getting treatment, correcting misconceptions, outcomes of early detection and treatment, and explaining the treatments' side effects would reduce presentation delay regardless of symptomatic or asymptomatic patients.

4.6.2.5 Conclusion of presentation delay

Factors associated to presentation delay in this study was study location; Kota Bharu. These factors illustrate that presentation delay was attributed to a multifactorial problems of socio-culture, patients behaviour, and poor breast health literacy among patients. The associated factors as stated above indicate that delayed presentation can be improved. Based on the time intervals in the breast cancer journey, we can reduce the time taken to presentation by reducing the 'Presentation Interval' where the patients may actually identify symptom and seeking help much earlier. Hence, there is an urgent demand to provide culturally appropriate programs which improve the breast health literacy among patients' knowledge of how to practice breast awareness and adopt positive help-seeking strategies especially in that particular location; Kota Bharu, Kelantan. Thus, an update to the 'Breast-Self Examination' guideline is needed to improve the quality of breast cancer care in Malaysia.

4.6.3 Diagnosis delay

4.6.3.1 Diagnosis details amongst patients attending public hospitals in Malaysia

Time to diagnosis in this study was divided into 4 intervals; referral, biopsy, report and disclosure. Findings showed that referral interval was the longest interval with a median time of 8 days (range: 0 day – 8 months) as compared to 0 day (same day) from a study in Denmark (Hansen et al., 2011). No consensus or standardized time frame is suggested for referral from a primary care facility to a diagnostic center in Malaysia. However, 2 weeks was suggested for referral time in the UK and Ireland (Mccain et al., 2011; Ireland National Cancer Registry, 2012).

Public and private primary health care clinics may carry out initial diagnostic investigations or refer patients to the diagnostic centre, thus transferring further responsibility to secondary health care system (Hansen et al., 2011). In this study, the main functions of primary care facility are referring patients with symptoms of breast cancer to the hospital, either through surgical or breast clinics that serve as diagnostic centres. Very few of the primary care facilities in this study initiated diagnostic investigations and most of the investigations were carried out in the hospital settings. More importantly, we found that those who have been referred from a hospital department (e.g. OPD, A&E) was seen to have longer referral time than those who were referred from a primary care facility (e.g. public or private clinics) outside of the hospital. Some initial investigations were carried out at the hospitals department requires multiple visits by patients before being referred to the diagnostic center may lead to a longer referral duration. This suggests that the first health service contacted would determine the patients' navigation process and the referral interval. However, referral interval was not an independent factor for diagnosis delay in this study.

The median time to first biopsy in this study was 0 day (range: 0 days – 20 days), where most patients underwent first biopsy at their first visit to diagnostic centre. The ideal method for diagnosis of breast cancer is still debatable. Core needle biopsy (CNB) (81.5%) was the commonest mode of biopsy in this study, in contrast to an old study conducted in UMMC where fine needle aspiration cytology (FNAC) (55.5%) was the commonest biopsy performed (Tham et al., 2009). Our finding is supported by a study where CNB is currently replacing FNAC in many centres as a diagnostic tool in breast cancer diagnosis (Pilgrim & Ravichandran, 2005). This could be explained as interpretation of CNB is basic skill of pathologist and does not require expertise in cytology. CNB has improved microcalcification diagnosis and has a higher sensitivity and specificity compared to FNAC (Chuo & Corder, 2003; Pilgrim & Ravichandran, 2005). However, the choice between fine needle aspiration and core biopsy could be based on its audited results (Chaiwun & Thorner, 2007) and availability of expertise in the diagnostic centre, as well as the physical characteristics of the lump (Tham et al., 2009).

Histopathological examinations (HPE) in this study took a median time of 7 days (range: 3 days – 3.5 months) to report a result. Little is known about the practice of multidisciplinary team meetings in the six hospitals except for UMMC where majority of biopsies taken were discussed at a weekly multidisciplinary team meeting and definitive diagnoses were reached with the agreement of all team members (Tham et al., 2009).

Generally, patients in this study were seen to receive the confirmed diagnosis or disclosed about the diagnosis during their follow-up visit which took an additional median time of 4 days (range: 1 day – 1.8 months) from the report date. During the follow-up visit, patients were informed about the diagnosis as well as the treatment plans.

Majority of the patients in this study were diagnosed at the studied hospitals, indicating that the public health services play a major role in seeking a diagnosis. About 45% of patients in this study were diagnosed at stage III or IV. This is consistent with the national cancer registry report (Zainal Ariffin & Nor Saleha, 2011) and previous studies which reported that 30-60% of new cases were diagnosed at late stages disease in Malaysia (Cheng et al., 2015; Norsa'adah et al., 2012; Taib et al., 2007; Taib et al., 2011). In this study, Malays (27%) shows the highest rate of late stage disease which is similar to other studies (Cheng et al., 2015; Taib et al., 2013). Although the factors for late stage disease are not studied in this study, we believe that this could be related to the hetereogenity of cancer biology where Malay patients were found to had more aggressive and high grade tumors compared to other ethnicities (Nirmala Bhoo-Pathy et al., 2012).

In this study, we found poor timeliness of referring patients to the diagnostic centre as compared to western studies. Efforts to reduce diagnosis time in Malaysia concentrating on referral interval should be conducted with propose timeframe. Since this is the first study carried out thoroughly on the timeliness of diagnosis in Malaysia, as well as the different time points used between other studies, comparison of time to biopsy, reports, and disclosure between studies are difficult.

4.6.3.2 Time interval between presentation to primary healthcare and resolution of diagnosis amongst patients attending public hospitals in Malaysia

The median time to diagnosis in this study was 26 days. In comparison to other studies in Malaysia, our finding was longer than 9 days from a study in Kuala Lumpur (Lim et al., 2014) but shorter than 5.5 months from a study in East Coast (Norsa'adah et al., 2011). The diagnosis interval discrepancy could be due to differing measurement points,

screening practices, health seeking behavior, patient compliance and health resources available in a health care institution (Taib et al., 2007).

In comparison with other countries, our finding was consistent with 21-28 days from studies in Thailand and Taiwan (Poum et al., 2014; Shieh et al., 2014) and 16-32 days from studies in developed countries (Caplan et al., 2000; Plotogea et al., 2014; Ruddy et al., 2014). Therefore, findings illustrate that time to diagnosis of breast cancer in Malaysia is acceptable but still need room for improvement especially on referral interval.

4.6.3.3 The proportions of delays in diagnosis amongst patients attending public hospitals in Malaysia.

The proportion of diagnosis delay in this study was 41.8%. It was consistent with 42% from study in Thailand (Poum et al., 2014) and better than 60.7-70% from studies in China and Libya (Ermiah et al., 2012; Huo et al., 2014). However, in comparison with other developed countries, our figure was much higher than 6-16% from studies in US and UK (Macleod et al., 2009; O'Rourke, 2012; Ruddy et al., 2014). This illustrates that diagnosis delay amongst the breast cancer patients was high and is a serious problem in Malaysia.

4.6.3.4 Factors associated with diagnosis delay

This study explores the delay in diagnosis among breast cancer patients by trying to determine the factors associated with delay in getting a diagnosis resolution after presenting to a primary health care. The discussion throughout this section will be guided by exploring the barriers in getting a diagnosis among breast cancer patients in Malaysia.

Results in this study showed that symptom without breast lump was significantly associated with diagnosis delay, similar to other studies (Forbes et al., 2014; Plotogea et

al., 2014). The absence of symptoms such as lump or pain may lead patients towards non-recognition of breast cancer symptoms and unawareness of being at risk (Norsa'adah et al., 2012; Taib et al., 2011; Taib et al., 2014). This illustrates that the presence of lump was an important feature for the interpretation of breast cancer among patients in Malaysia. Therefore, thoroughly imaging investigations and image-guided biopsies are suggested in a timely manner. Although patients present with a lump, a systematic review has reported that false assumption of breast lump as benign, lack of clinical breast examination (CBE) efficiency in early detection, did not refer the patients for further investigation, and poor communication between primary health care providers and patients may compound this further (Lim et al., 2015; Taib et al., 2011; Yu et al., 2015). This study suggests that poor breast health literacy among patients and incompetence of healthcare providers in detecting possible breast cancer symptoms will cause patients to have difficulty for early diagnosis as seen in other studies (Bish et al., 2005; Burgess et al., 1998; Taib et al., 2011; Forbes et al., 2014).

Inconclusive biopsies that needed open surgical biopsies was associated with diagnosis delay as seen in other studies (Bairati et al., 2007; Plotogea et al., 2014). Patients undergoing surgical biopsy had significantly longer duration to diagnosis compared to needle biopsy, suggests that type of biopsy is a predictor to delayed diagnosis for symptomatic breast cancer. In Malaysia, surgical biopsy was considered as the last option which was carried out only after many inconclusive biopsies (Ministry of Health Malaysia, 2010), may explains to this finding. To reduce delay in diagnosis, image-guided sampling by both cytology and core biopsy is recommended to be used, where facilities and expertise are available (Barber et al., 2004; Bright et al., 2011).

In addition, those who had undergone 2 or more biopsies had longer diagnosis duration compared to those with 1 biopsy as seen in another study (Baliski et al., 2014).

Diagnostic errors may occur during the performances of biopsy procedure or the interpretation of the pathological report. As more false-negative diagnostic tests or suspicious results are extracted, more biopsies are needed to be carried out (Bairati et al., 2007), thus taking much longer time for the pathological services to confirm malignancy. Consequently, the additional number of biopsy procedures prior to confirmation of diagnosis leading to delayed diagnosis.

As opposed to delay in presentation, delay in diagnosis was not significant with late stage cancer. The diagnosis of breast cancer in Malaysia is typically confirmed by a standardized protocol of triple assessments based on examination, imaging, and biopsy (Ministry of Health Malaysia, 2010). Patients undergo these assessments regardless of their clinical presentation, either symptomatic or asymptomatic cancer. Findings show that cancer stage at diagnosis was not affected by time to diagnosis due to shorter diagnosis interval. This is supported by other studies which reported that delay in diagnosis was not being associated with late stage cancer (Shieh et al., 2013; Tartter et al., 1999). A long duration of more than 6 months may be considered as an indicator of tumor progression (Fujii et al., 2015). Even though the tumors were significantly larger at the time of diagnosis, cancer outcomes are based on the frequency of nodal involvement (Tartter et al., 1999) and aggressiveness of tumor (Bloom, 1965), explaining that cancer outcome was not significantly affected by diagnostic delay.

The role of screening program and practice of mammograms in reducing diagnosis waiting times is still found to be conflicting. A study conducted in the UK reported that screened women were diagnosed and treated more quickly than symptomatic women (Allgar & Neal, 2005) while in contrast, some studies reported that women with screen-detected cancer had longer times to diagnosis than those presenting with symptomatic cancer (Brett et al., 1998; Burgess et al. 1998; Bairati et al., 2007). Therefore, the method

of detection was not included in the analysis since all patients in this study were symptomatic breast cancer and none of them were detected through mammographic screening. This is supported by other study which reported that majority of breast cancer patients in Malaysia had detected through self-detection (e.g. BSE, CBE) while a small percentage had detected through mammographic screening (Yip et al., 2006). The breast screening facilities in Malaysia is still underutilized (Dahlui et al., 2011). No population based screening program conducted in Malaysia (Yip et al., 2006). However, to encourage women to undergo mammogram screening for early detection of breast cancer, the Ministry of Women Family and Community Development (MWFC) Malaysia (LPPKN, 2014), had launched a subsidise program for every mammogram done in private clinics and hospitals registered with the National Population and Family Development Board Malaysia (NPFDB) or known as Lembaga Penduduk dan Pembangunan Keluarga Negara (LPPKN, 2014). Although this subsidised mammogram program is still early and requires a lot of improvements, it is a good effort that plays an important role in promoting early detection of breast cancer in Malaysia.

Previous studies had reported that marital status (Neal & Allgar, 2005) and socio-economic (Bairati et al., 2007) were significant to diagnosis delay. Married patients are more likely to discover breast abnormalities through their spouse, and getting diagnosis promptly as having emotional and economic support from their spouses. Meanwhile, the divorced and widowed are more likely to experience extensive financial burden and family responsibilities, which consequently leads to a delay in diagnosis (Shieh et al., 2013). However, these two factors were not significant in this study. Since there is a high accessibility of medical care in Malaysia and public hospitals provide minimum or highly subsidised healthcare (Norsa'adah et al., 2012), it is believed that socioeconomic status is unlikely to be the factor for delay in diagnosis.

4.6.3.5 Conclusion of diagnosis delay

Factors associated to diagnosis delay in this study were symptoms without breast lump, underwent two or more biopsies and surgical biopsies. These factors illustrate that diagnosis delay was attributed to a multifactorial problems of fear on diagnostic test, poor breast health literacy among patients, incompetency of health care providers and referral issues. The associated factors as stated above indicate that delayed diagnosis can be improved. Based on the time intervals in the breast cancer journey, we can reduce the time taken to a diagnosis by reducing the 'referral interval' where the patients may actually refer to a diagnostic centre much earlier through a systematic referral procedures. Hence, there is an urgent demand to provide efficiently training programs to the primary health care providers especially on skills of how to conduct a proficient breast examination and adopt effective communication abilities. In addition, an update to the 'Clinical Breast Examination', referral time and diagnostic time guidelines are needed to improve the quality of primary and secondary health care in Malaysia.

4.6.4 Treatment delay

4.6.4.1 Treatment details amongst patients attending public hospitals in Malaysia

Surgery is a main breast cancer treatment with 86% of patients in this study successfully underwent surgery as seen in another study (Lim et al., 2014) which indicates high accessibility to breast surgery at public hospitals in Malaysia. It was seen that a large proportion of patients underwent mastectomy (MAC) than breast-conserving surgery (BCS), similar to other local studies (Bhoo-Pathy et al., 2014; Teh et al., 2014), illustrates that MAC is the commonest type of breast surgery among Malaysian patients. MAC rates in this study was 63% as compared to 31% in United States (Katipamula et al., 2017),

whereas BCS rates in this study was 34% as compared to 60% in United States (Lazovich et al., 1999). This indicates that BCS is more common in developed countries, while MAC is more common in developing countries. Larger tumor size at presentation (Yip et al., 2006), surgeons preferences, smaller breast volume in Asian women (Teh et al., 2014) and patients choice (Bhoo et al., 2011) were the reasons for higher MAC rate. Besides, the Asian cultural factors in older patients accept MAC since they have completed their families, breastfed their children, and are less concerned with their physical appearance (Wong et al, 2008; Gumus et al, 2010) while, younger patient may opt for MAC to feel safer, have financial constraints (Leong et al., 2007) and to avoid radiotherapy (Corradini et al., 2014). Nevertheless, BCS became the preferred choice of surgery in western settings (Lazovich et al., 1999), BCS is an accepted surgical technique for treatment of breast cancer in Malaysia (Ministry of Health Malaysia, 2010).

Although there was good adherence of breast surgery and those who needed surgery could receive it within a short waiting time, the performances of chemotherapy and radiotherapy were low. Non-adherence rate for chemotherapy and radiotherapy (30% and 33%) seen in this study were higher compared to another local study in an urban setting (25% and 19%-23%) (Lim et al., 2014). More expertise and better physical infrastructure involved in the other study may explain the differences to these findings. Meanwhile, a broad range of non-adherence to chemotherapy (25% to 80%) according to study locations was seen with patients in Perak and Kelantan shows the highest rate of non-adherence. A possible explanation is due to unavailability of oncologist at these hospitals, as well as socio-cultural and socio-economic related factors.

In this study, hormonal therapy showed the highest proportion of non-adherence at 1-year post diagnosis (36.3%) and was higher than the other published literatures (16-28%) (Aalto, 2013; Brito et al., 2014; Hershman et al., 2017; Kimmick et al., 2017; Kirk

& Hudis, 2008). This figure is worrying as it was measured at the first year of diagnosis compared to 32% in 4.5 years of diagnosis in United States (Hershman et al., 2017), illustrates a poor adherence of hormonal therapy amongst breast cancer patients in Malaysia.

The reasons for non-adherence in this study were patient's refusal for treatment (14.5%), incomplete or stopped treatment for non-medical reasons (8.2%), and missed going to hospital (7.3%). This figure could be higher as it was reported that 25% of those who discontinue their medicine entirely do not inform their doctors (Aalto, 2013). Therefore, findings highlights the need for sensitivity of oncologists and health providers to provide information on benefits and side effects that is understood by patients as well as providing psycho-social support which may increase the adherence rate of oncology therapy.

This study suggests that non-adherence to cancer treatments is a serious problem in Malaysia. The performance of breast surgery was good but not for oncology therapy; chemotherapy, radiotherapy and hormonal therapy. Therefore, factors contributing to delay and non-adherence should be sought to improve this situation and interventions put in place urgently.

Based on the 'Total Breast Cancer Delay' model by Taib et al. (2014), there is a modified stage known as 'treatment decision delay' by patients in the post-diagnostic phase. However, this interval was not measured in this study as data on treatment decision date was not recorded prospectively and was difficult to be recalled by the patients. Moreover, some of the treatment decisions were not made by the patients themselves but their family members which are consistent with the family-oriented culture in Asia (Muhamad et al., 2012; Teh et al., 2014). Therefore, it is believed that this interval is subjective and much suitable for a qualitative study.

4.6.4.2 Time interval between the diagnosis resolution and initiation of treatment amongst patients attending public hospitals in Malaysia

The median time to initial treatment in this study was 21 days. In comparison to other studies, our finding was longer than 11 days from a study in Kuala Lumpur (Lim et al., 2014) but consistent with 17-29 days from studies in US (Bustami et al., 2014; Connors et al., 2014; Sasha et al., 2013; Plotogea et al., 2013; Caplan et al., 2000). Therefore, findings illustrate that time to initial treatment of breast cancer in Malaysia is acceptable but still need room for improvement.

The time to surgery, chemotherapy, radiotherapy, and hormonal therapy after diagnosis were 22 days, 57 days, 190 days and 212 days respectively in this study which was much longer as compared to 11 days, 51 days, 194 days and 171 days respectively from a previous study conducted in Kuala Lumpur (Lim et al., 2014). A possible explanation to this finding is due to the type of hospitals, where the study consist of a mixture of university and private hospitals which had many expertise and technologically advanced equipment compared to public hospitals, hence explaining the differences between these two studies.

4.6.4.3 The proportions of delays in treatment amongst patients attending public hospitals in Malaysia.

The proportion of treatment delay in this study was 35.3%. It was higher than 21.9% from a previous study conducted in a university hospital of UMMC (Mujar et al., 2013). This was supported by another study which reported that better interval was found in university hospital than general hospital due to better expertise and modern facilities (Brazda et al., 2010) thus, explaining to the findings differences. In comparison with studies in other countries, our figure was higher indicating that treatment delay was high

among breast cancer patients utilizing public hospitals in Malaysia (Connors et al., 2014; Sasha et al., 2013; Yau et al., 2010).

4.6.4.4 Factors associated with treatment delay

This study explores the delay in treatment among breast cancer patients by trying to determine the factors associated with delay in getting a treatment after diagnosed with breast cancer. The discussion throughout this section will be guided by exploring the barriers in getting an initial treatment among breast cancer patients in Malaysia.

Treatment delay varied by location and patients in Kuala Lumpur, Johor Bharu, Kota Bharu and Kuching who getting treatment at Hospital Kuala Lumpur, Hospital Sultan Ismail, Hospital Raja Permaisuri Zainab and Hospital Umum Sarawak were the independent factors for treatment delay in this study. We believe that treatment delay is primarily influenced by the type of hospital, whereby these significant centers were the public hospitals as compared to a university hospital of University Malaya Medical Centre which has many expertise, high technologically equipment, and modern facilities. A longer treatment interval was seen in the general hospital compared to the university hospital (Brazda et al., 2010). Meanwhile, patients in Kelantan showed the highest risk of treatment delay compared to other locations in this study. This supported by a qualitative study conducted in Kelantan which reports a longer median time to treatment of 1.2 months (Norsa'adah et al., 2012). The health seeking pattern among women in Kelantan is attach together with their husbands' decision, reflecting the couple perspective in seeking the right choices of treatment for breast cancer (Yusoff et al., 2011). Therefore, study finding suggests that the health system hierarchy between health institutions and social-culture norm between locations play an important role in treatment delay among breast cancer patients in Malaysia

Study findings showed that those who were diagnosed at other hospitals than treating hospitals have a higher risk to delay treatment, similar to other Asian studies (Chen et al., 2015; Yoo et al., 2016). We believe that longer time is taken to refer a patient from one hospital to another hospital. Referring patient and scheduling for treatment required longer waiting time and highlighting limitation in navigating patients between hospitals. However, this situation is unavoidable as it involves many aspects such as availability, accessibility, accommodation, affordability, and acceptability to treatment (Unger-Saldaña, 2014). Moreover, most patients fear that their cancer will progress during the prolonged treatment time (Yoo et al., 2016) and may have different and conflicting opinions with their care providers in balancing the need of referring to another hospital or timely treatment based on adequate informed consent (Landercasper et al., 2010). Therefore, navigating patients to treating facilities is vital in guiding the patients and their families to shorten treatment delays.

Treatment delay was also attributed by the patients who are poor in making treatment decision as seen in other local qualitative studies (Abdullah et al., 2013; Taib et al., 2014; Yusoff et al., 2011). After a diagnostic resolution, the newly diagnosed breast cancer patients are confronted with some unavoidable stressful interval and thus experiencing emotional instability (Yoo et al., 2016). This psychological stress would affects to negative perceptions about breast cancer treatment and led to delay in making treatment decision and non-adherence of cancer treatment (Lim et al., 2015; Pérez et al., 2008). Studies showed that knowledge and social support helps patients to understand their diagnosis and assists patients in making treatment decisions early (Butow et al, 1997;. Thibodeau et al, 1997; McWilliam et al, 2000) and helps patients in getting a sense of control over their condition, reduce anxiety, changing behaviour and drawing up plans for the future (Henman et al., 2002). However, social support by the family members and care providers were seen to be poor (Taib, et al., 2011; Unger-Saldaña & Infante-

Castañeda, 2011). Lack of self-management, lack of family support especially husband, too reliance on family decision (Taib et al., 2011; Norsa'adah et al., 2012; Taib et al., 2013; Yu et al., 2015), poor psychosocial support from psycho-oncologists and clinical nurse specialists (Taib et al., 2014), and ineffective communication between patients and health care providers (Abdullah et al., 2013; Taib et al., 2014) would influence on cancer care. Thus, attention and involvement of family members and training for surgeons and oncologist in sensitive communication skills focusing on breaking bad news, communication of risk and recommended treatment using the collaborative decision-making approach are required (O'Grady & Jadad, 2010; Taib et al., 2014).

No association was found between treatment delay and stage of cancer in this study. This indicates that the severity of cancer do not determine the time in getting an initial treatment at public hospitals in Malaysia. Treatment interval did not differ according to cancer stage (Wagner et al., 2011; Yoo et al., 2016). However, in contrast to our finding, another study have found that the advanced stages of cancer were associated with shorter time to treatment and patients diagnosed at stage III has a shorter waiting time for surgery (Plotogea et al., 2013).

The lack of experts in public hospitals in Malaysia did not affect the time taken to treatment of breast cancer. Hospitals without breast surgeons or medical oncologists in this study did not predict the treatment delay. This illustrates that there is no different on the timeliness of treatments either the hospitals with or without the specialists or experts. We believe that cross-referral between the hospital departments of surgical, oncology and radiation centres may be attributed to the prolongation of treatment interval. A study by Yoo et al. (2016), had supported our findings which reported that the additional biopsies, patients navigation, clinical consultation with other departments and hospitalization prior to treatment attributed to longer duration of treatment. Besides, type of surgery also

played a significant role as more delay was seen among patients with total mastectomy than those with breast-conserving surgery and reconstructive surgery in another study (Wagner et al., 2011).

Studies in United States showed that living far away from the treatment centre, on vacation, and too busy with other things were the reasons for treatment delay (Bish et al., 2005; Caplan et al., 2000; Facione & Facione, 2006). Similarly, our patients who undergoing spiritual and religious tours like performing umrah, praying in the Ganges river, visiting temples in China and other spiritual tours could be the reasons for treatment delay. Therefore, it emphasizes the importance that each country should undertake their own studies regarding the factors and reasons of treatment delay so that effective health promotion programs like 'patients decision aids' can be formulated in accordance with the social and cultural settings.

4.6.4.5 Conclusion of treatment delay

Factors associated to treatment delay in this study were location and diagnosis place. These factors illustrate that treatment delay was attributed to a multifactorial problems of locality variations, social culture, patients' navigation, psychological barriers and poor social support. The associated factors as stated above indicate that delayed treatment can be improved. Based on the time intervals in the breast cancer journey, we can reduce the time taken to treatment by reducing the 'Treatment interval' where treatment decision could be made much earlier through a collaborative decision-making approach between the patients and health care providers. Hence, there is an urgent demand to improve social support of the family members and training oncology health care providers in effective communication skills, thus minimize the treatment delay and improve the quality of tertiary health care in Malaysia.

4.6.5 Non-adherence to breast cancer treatment

4.6.5.1 The factors associated with non-adherence to surgery

Study findings showed timely services and high adherence to surgery at public hospitals in Malaysia as seen in previous study (Lim et al., 2014). Study locations were associated with non-adherence to surgery and patients from Kuala Lumpur, Johor Bahru and Kota Bharu were at higher risk to default surgery. Similar to treatment delay, we believe it could be due to the type of hospital whereby university hospital composed with many expertise, high technology equipment, and modern facilities, thus making good accessibility to surgery.

Meanwhile, in comparison to other locations, patients in Johor Bahru and Kota Bharu showed the highest risk of non-adherence to surgery. The reasons for non-adherence to surgery among patients in this area has not been studied but is believed to be related to the local culture of a family-oriented social structure community (Muhamad et al., 2012; Norsa'adah et al., 2012). The influence of partners and family members play an important role in making treatment decision for surgery (Karbani et al., 2011; Teh et al., 2014). These factors include influence of patient's spouse or family members, culture or traditional practices, and medical pluralism (Taib et al., 2014). Therefore, the complex interplays between local social culture affects the poor adherence of surgery was illustrated in our findings. Hence, the need for surgeons and health practitioners' sensitivity are crucial in dealing with patients for surgical options especially involving the two localities mentioned. Further study on overall survival should be conducted to give a clearer picture of the outcome or impact of non-adherence to surgery. Therefore, prompt action with comprehensive planning could be taken to reduce non-adherence to surgery.

There was an increasing number of patients refusing mastectomy (MAC) as seen in other studies (Micliorelli, 1978; Teh et al., 2014). Those who need mastectomy (MAC) in this study were at higher risk to refuse surgery than breast-conserving surgery (BCS). The increasing number of patient refusing mastectomy is possibly related to the Asian culture whereby MAC could impact the wife-husband relationship since it affects sexuality and body image of a woman (Norsa'adah et al., 2012). Malaysian local communities are affected by the traditional system in which patients' decision and actions are controlled by the man in a family, especially by the husbands (Ednin, 2007). Post-mastectomy may cause low self-esteem, thus leading to fears of abandonment by their husband or partner (Facione & Facione, 2006). Therefore, this finding illustrates that the strong social culture in Malaysia that compels women to delay by refusing mastectomy to avoid disruption of the well-being of their family and as an alternative measure, they may seek other methods which may preserve the breast.

The lack of surgeon in public hospitals in Malaysia did not impact the non-adherence to breast surgery, illustrates that there is no different either the hospitals with or without the specialists or experts. We believe that it would relate to the emotional and psychological disturbance as reported from the other studies. Fear of MAC (Ibrahim & Oludara, 2012), negative perceptions on MAC (Bish et al., 2005), pain (Burgess et al., 1998) and suffering the disfigurement after MAC (Mohamed et al., 2005) were the factors of why women avoids MAC. Besides that, prolonged denial may prevent patients from getting appropriate management by defaulting appointments, non-compliance and refusing treatment (Andrews and Bates, 2000).

Therefore, an intervention study is needed to reduce non-adherence to surgery. Effective communication between patients and health professionals as well as social support from the family members could lead to adherence as certain time period is needed

by patients to accept the diagnosis of breast cancer and its treatment especially for those who required mastectomy (MAC).

4.6.5.2 The factors associated with non-adherence to oncology therapy

Findings found that study location was associated with non-adherence whereby patients from Ipoh, Perak were at a higher risk to default oncology therapy. The association between patients in Perak and non-adherence to oncology therapy could possibly be due to lack of oncology services in the same hospital. Those who required for oncology therapy were referred for treatment to another hospital in Kuala Lumpur or Penang, suggesting difficulties in terms of travelling expenses, logistics, accommodation and emotional support. These difficulties would possibly lead patients to defaulting appointments, non-compliance, delaying and refusing treatment.

The lack of oncologist in public hospitals in Malaysia did not impact the non-adherence to oncology therapy. Findings from other studies had reported that financial status, fear of subsequent operation, unbearable side effects, missed appointments, inadequate follow-up, and complementary and alternative medicine (CAM) use were the factors for non-adherence to chemotherapy (Adisa et al., 2008; Steve, 2008; Chui et al., 2014; Taib et al., 2014), while intense follow-up, frequent commuting to the hospital and financial status are the factors for non-adherence to radiotherapy (Bhoo et al., 2011; Leong et al., 2007). Meanwhile, younger age group (< 50 years), diagnosed at advanced stage, alcohol drinkers, African American descent, economic status, received chemotherapy, shorter prescription refill intervals, adverse effects, more hospitalizations, poor communication between physician and patient and use combined tamoxifen and aromatase inhibitors are the factors for non-adherence to hormonal therapy (Brito et al., 2014; Hershman et al., 2017; Partridge et al., 2003). These findings demonstrate that despite having more specialized care, other supportive care e.g. emotional and

psychological support should be provided in public specialist hospitals in Malaysia. Besides that, the availability, accessibility, accommodation, affordability, and acceptability to treatment may also lead to non-adherence of oncology therapy. A comprehensive study is needed to evaluate non-adherence to each treatment modalities; chemotherapy, radiotherapy and hormonal therapy in the future.

4.6.5.3 Conclusion of non-adherence to breast cancer treatments

Factors associated with non-adherence to breast cancer treatment in this study were locations and those required mastectomy (MAC). These factors illustrate that non-adherence to treatment was attributed to multifactorial problems of hospitals hierarchy, social culture, sexuality and body image issues, psychological disturbance and treatment navigation. The associated factors as stated above indicate that non-adherence to treatment can be improved.

Hence, there is an urgent demand to provide community educational programs focusing on correcting misconceptions, outcomes of treatment and treatments' side effects would reduce non-adherence to breast cancer treatment and improve the quality of cancer care in Malaysia.

4.7 Limitations

The results may be affected by the small sample size. Since sampling was based on the list of newly diagnosed breast cancer and the availability of medical records, the researcher has no control over this. Difficulty in obtaining all medical records may have excluded patients who experienced delays in presentation, diagnosis or treatment. However, every precaution and resources were utilized to obtain all breast cancer patients, hence a retrieval rate of 39% in busy public hospitals with limitations in manual records keeping gives a good representation.

In addition, selection bias may occur as the study was conducted only in public hospitals, where a majority of the patients were Malays whereas the highest ethnic group affected by breast cancer in Malaysia was Chinese (Zainal Ariffin & Nor Saleha, 2011). This could be explained by the relatively lower attendance of Chinese patients to public hospitals (Institutes for Public Health, 2008).

The reliance to only use medical records or database registry limit the quality of information and was potential for reporting bias. The term reporting bias is used to refer to people's tendency to under-report all the information available (Gordon & Van Durme, 2013). All possibilities such as misinterpretation, misinformation, incomplete information, fuzzy texts, and difficult to read or interpret are among the biased reports. Besides, only the available data can be used. Therefore, to overcome this problem additional interviews were conducted to complete any missing data. The data was then cross-validated between the medical records and patient interviews by the researcher to ensure for data accuracy and validity.

The sampling method in this study with regards to hospitals participation had intended to select hospitals which could represent the geographical regions in Malaysia. However, since the agreement of the breast surgeons in the respective hospitals were required and unfortunately not all hospitals had agreed to participate, statistically the sampling could not really represent to the Malaysian breast cancer patients in general. But since most of the main hospitals in the study location (e.g. Kuala Lumpur, Perak, Johor, Kelantan, and Sarawak) are tertiary hospitals and in different regions of the country, the findings obtained are relevant for the clinicians and the policy makers in the management of the breast cancer in Malaysia. Nevertheless, the results presented in this study only describe the differences of the breast cancer patients and health systems from these hospitals in various locations in Malaysia.

There are differences in defining and categorizing delay. Most studies used different cut-off points for delay and each researcher used different measurement points to measuring delays. No standardized measurements have been formed to calculate delays. However, we attempted to minimize this by using the cut-off points which formally and commonly used in other studies for presentation, diagnosis and treatment delay (Ghazali et al., 2013; Harirchi et al., 2005; Montazeri et al., 2003; Unger-Saldaña & Infante-Castañeda, 2009). Nevertheless, fair comparisons were possible and the findings were valid.

There also appears to be large variation of delays (e.g. presentation, diagnosis, treatment) and non-adherence (e.g. surgery, oncology therapy) by locations. The adjusted coefficient and adjusted odd ratios for non-adherence seems larger than delays. However, this studied factor does not explain away the variation. The possible reason for this variation is the different number and type of covariates adjusted for in the final multivariable model. Besides, finding also showed that cancer stage and presentation delay is confounded. However, the analysis was limited to univariable model only. The noticeable limitation is this section was not part of the study objectives but only act as additional information thus, multivariable model was not done. Cancer stage and delays could be another interesting study topic which if conducted in this study could be very time consuming.

This study did not explore the other aspects of behavioral, cultural and accessibility to healthcare services. More interventional and geographical studies are required in the future to evaluate and improve delays and non-adherence problems. Future directions in research should entail a deeper understanding besides identifying the underlying reasons associated with delays of breast cancer in Malaysia while health policy has to clearly define the period for presentation, diagnostic and treatment

indicators. The practice of community education programs and training oncology health care providers in communication skills and collaborative decision-making are recommended.

4.8 Strength

The information or data obtained in this study is highly valid since careful extraction of data had been made by the researcher. Data were collected through written evidences with support from the medical records to minimize recall bias. Actual dates of events and all clinical information written in the medical records were used for accuracy. Meanwhile, interviews were conducted to obtain additional patients information and missing values in the medical records. The data was then cross-validated between the medical records and patient interviews by the researcher to ensure accuracy. Therefore, the validity and precision of the data collected were determined.

To the best of our knowledge, this is the first study to examine the complete intervals of breast cancer journey starting from symptom discovery until treatment initiation. This study thoroughly measured the length of time between important time points of the breast cancer journey, and associated factors to delays in presentation, diagnosis, and treatment. Besides that, this study is the first study to report a nationwide evaluation on the non-adherence to breast cancer treatments. There are few studies performed on non-adherence towards breast cancer treatments, especially hormonal therapy which had never been documented before in Malaysia.

This study was a multicenter study which was conducted at six public hospitals and covered all the regions in Malaysia (e.g. Central, Northern, Southern, Eastern, and East-Malaysia). All participating hospitals are tertiary hospitals which are the main hospital in the region and act as a referral centre for breast cancer patients, making it relevant for clinicians and the policy makers in the management of the breast cancer in

Malaysia. Besides, this study widely recruited patients from the diverse socio-demographic and multi-ethnic backgrounds to provide a better picture of breast cancer, thus making it possible to infer the findings to all breast cancer patients in Malaysia.

4.9 Contribution and Implications of the study

4.9.1 Clarity of time intervals of important time points in the breast cancer journey

The time intervals in the breast cancer journey is an improvement of the 'Total Breast Cancer Delay' model (Taib et al., 2014) to clarify the trajectory of the breast cancer journey to simplify data collection to measure delays. By explicitly placing the trajectory of the breast cancer journey in a simple measurable form, designing studies on time delays was made clearer.

4.9.2 Measuring performance of presentation, diagnosis and treatment of breast cancer

This study illuminates the stages of patient and health system delay. Currently, there are no indicators to audit performances of patients and health system. The time intervals in the breast cancer journey could be as a performance indicator in hospitals providing diagnostic and treatment services, thus assist public health policy makers for future planning. It is important to identify the delay time points as an audit indicator to justify resources to be diverted and to adopt strategies and guidelines to guide practice.

The recent Clinical Practice Guidelines published in 2010 (Ministry of Health Malaysia, 2010) provide great emphasis on treatment based indicators. A single proposed performance indicator in timely treatment within 2 months of presentation into a diagnostic facility is as included below (Fig. 4.14). However, there is no emphasis on

suggestion period for patients and diagnostic indicators. Therefore, 3 months, 1 month and 1 month are suggested for the patients, diagnosis and treatment indicators respectively.

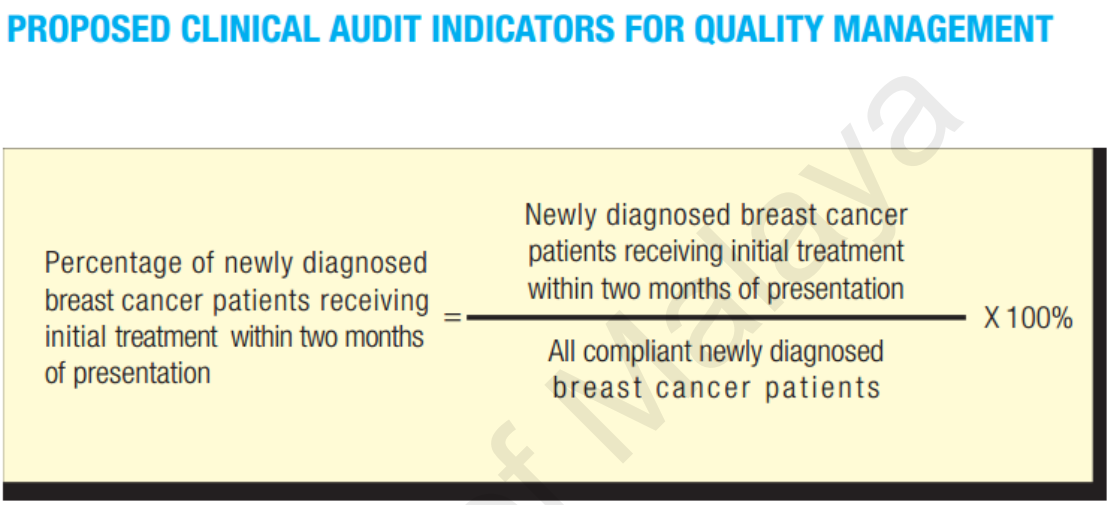


Figure 4.14: Proposed clinical audit indicators for quality management from the Clinical Practice Guidelines Malaysia (2010)

Source: Reprinted from "Management of Breast Cancer Clinical Practice Guidelines Malaysia" by Ministry of Health, Malaysia (2010).

4.9.3 Navigating patients in breast cancer journey

Navigating through the breast cancer journey is challenging as there are no clear-cut pathways as well as dedicated services to pave the way. Therefore educating the public about the time intervals in the breast cancer journey are important and a clear pathway to breast cancer journey from one stage to the another could play a significant role to the public as a source of information as well as to improve the health seeking efforts, diagnostic resolution, and treatment adherence among breast cancer patients.

4.9.4 Health education and awareness for the public

Through this study, we found a poor level of literacy in breast health especially in symptoms of breast cancer. An urgent intervention is needed in the primary health care settings for general practitioners, obstetricians, midwives, nurses or other health providers when consulting women seeking help for breast changes. Education on breast changes and signs, disease progression and disease outcomes must be informed to women as it helps in decision making and to prevent patients from thinking that cancer can be successfully controlled if they are on complementary and alternative medicine. Public education can be improved by providing adequate information about breast cancer. By providing relevant information to the public, the awareness of early presentation, diagnosis, and treatment of breast cancer can be expected within the community.

4.9.5 Culturally sensitive health care

Providing healthcare services in Malaysia is a challenge due to multi-ethnic, multilingual and various socio-demographic backgrounds of breast cancer patients. Therefore, training for effective communication is needed to all health care providers who provide services. Training a culturally competent health care provider would result in effective communication skills in delivering meaningful information and sensitivity to the disease. Better communication, provision of psychosocial, spirituality and instrumental support are required in keeping the needs of health care services in Malaysia.

4.9.6 Psychological support

Patients' literacy of breast health and socio-cultural factors play important roles in the interval prolongation and non-adherence to treatment. Health care professional was the important source of information and influence the patients in making a decision. To assist early decision making among patients, it would be best to not only giving information but also needs to be involved in the decision-making process, which is the ability of health

care providers to guide and coach the patients together with their family towards making a collaborative decision. Hence, psychological support approach may reduce delays and non-adherence among the breast cancer patients in Malaysia.

4.10 Conclusion

Delays in presentation, diagnosis, and treatment of breast cancer were prevalent among patients attending public hospitals in Malaysia. Breast cancer patients in Malaysia are generally taking longer time in help-seeking process but much earlier in getting a diagnosis and receiving treatment. Adherence to surgery is better compared to oncology therapy. Study found that delay in presentation, diagnosis and treatment, and non-adherence to oncology therapy were high and was a serious problem in Malaysia. Factors influencing delays and non-adherence are multifactorial implicating a complex interaction between strong influence of socio-culture, poor breast health literacy among patients and the health system. Therefore, an update on time to presentation, diagnosis and treatment guidelines and comprehensive intervention study like community educational programs aad training oncology health care providers in communication skills and collaborative decision-making are recommended.

4.11 Chapter summary

This chapter will be published in an article entitled “Presentation, diagnosis and treatment of breast cancer at public hospitals in Malaysia: The time intervals and factors associated with delays and non-adherence”. We found that complementary and alternative medicine (CAM) is widely used among the breast cancer patients in Malaysia. CAM use has been cited as a cause of delay in diagnosis and treatments in qualitative

studies (Nor'saadah et al., 2011; Taib et al., 2014). However, there had not been any confirmatory study that corroborates its impact on delays. Therefore, further study is important to evaluate the associated factors of CAM use and its relationship with delays in breast cancer among patients attending public hospitals in Malaysia, which is discussed in the next chapter.

CHAPTER 5: COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) USE AND DELAYS IN PRESENTATION, DIAGNOSIS AND TREATMENT OF BREAST CANCER PATIENTS ATTENDING PUBLIC HOSPITALS IN MALAYSIA

5.1 Introduction

Complementary and alternative medicine (CAM) is widely used among the breast cancer patients in Malaysia. CAM use has been cited as a cause of delay in diagnosis and treatments in qualitative studies (Nor'saadah et al., 2011; Taib et al., 2014), however there had not been any confirmatory study that corroborates its impact on delays. The purpose of this study is to determine the prevalence of CAM use and its relationship with delays in presentation, diagnosis and treatment of breast cancer among patients attending public hospitals in Malaysia.

This study is conducted to answer objective No.6. The data set used in the analysis was secondary data from main study (Chapter 4) which conducted to determine the proportion and factors associated with delays in presentation, diagnosis and non-adherence to treatment of breast cancer patients.

5.2 Study objective

To determine the associated factors of CAM use amongst breast cancer patients and its relationship with delays in presentation, diagnosis and treatments of breast cancer.

5.3 Literature Review

Complementary and alternative medicine (CAM) has become increasingly popular in Malaysia and widely used among individuals with cancer (Al-naggar et al., 2013) especially breast cancer patients (Muhamad et al., 2012). According to the National Center for Complementary and Alternative Medicine (2008), the term CAM is defined as a broad set of health care practices that are not part of a country's own tradition and not integrated into the dominant health care system. Complementary medicine is used in addition to conventional medicine, while alternative medicine is used as replacement of conventional medicine (Whitford & Olver, 2011).

Numerous studies had reported significantly high degree of CAM use in Malaysia. The prevalence of CAM use by breast cancer patients in Malaysia range from 25% to 88.3% (Chui et al., 2014; Chui et al., 2015; Knight et al., 2015; Norsa'adah et al., 2011; Raja et al., 2013; Saibul et al., 2012; Taib et al., 2007). High utilisation of CAM was also found in other Asian countries such as 75.0% in Indonesia (Azhar & Achmad, 2015), 67% in Korea (Hwang et al., 2015), 60.9% in Thailand (Puataweepong et al., 2012), 55.0% in Singapore (Chow et al., 2010) and 47.3% in Turkey (Tas et al., 2016).

There is no evidence claiming that complementary and alternative medicine (CAM) is more effective than conventional medicine but public opinion and interest in CAM is strong and growing. Although CAM has been reported to be commonly used among the breast cancer patients but its significance and implication to the efficacy of conventional medicine is still unclear (Abuduli & Aljunid, 2011; Chow et al., 2010). The efficacy of CAM has been found to be equal to allopathic medicine in the health beliefs of Malaysian breast cancer patients and has been found to be a cause of advanced stage at presentation (Taib et al., 2014). In Malaysia, about 30% to 56% of breast cancer patients present with advanced or stage III and IV disease (Leong et al., 2007; Norsa'adah

et al., 2011; Taib, Akmal, et al., 2011). Studies had found that delays is responsible for the advanced stage at diagnosis (Cheng et al., 2015; Ghazali et al., 2013; Ibrahim & Oludara, 2012), defaulting treatment (Leong et al., 2007) and by itself is a poor prognostic factor for breast cancer survival (Poum, Kamsa-ard, & Promthet, 2012; Richards et al., 1999; Taib et al., 2014).

To date, studies on CAM use amongst breast cancer patients in Malaysia are more focused on the prevalence and its associated factors (Al-naggar et al., 2013; Hasan, Ahmed, Bukhari, & William, 2009; Knight et al., 2015; Saibul et al., 2012), type and pattern (Farooqui et al., 2015; Raja et al., 2013), purposes (Muhamad et al., 2012), knowledge (Yew et al., 2015), and quality of life (Chui et al., 2015). There is a scarcity of published reports on CAM use and its impact on cancer treatments. The relationship of CAM use and delays in breast cancer has not been studied extensively. Association of CAM use and delays has not been investigated.

Hence, the objective of this study is to determine the prevalence of CAM use before treatment and its relationship with delays in presentation, diagnosis and treatments of breast cancer. Information from this study will assist clinicians and policy makers to formulate intervention strategies and implement public health activities that can reduce dependency of CAM and prevent delays in presentation, diagnosis and treatment of breast cancer in the future.

5.4 Methodology

5.4.1 Study approach

This study is a quantitative method approach.

5.4.2 Study design

This study is a multi-centre cross sectional study.

5.4.3 Study population

The study population consisted of all newly diagnosed breast cancer patients attending public hospitals in Malaysia.

5.4.4 Sampling method

Universal sampling design. All newly diagnosed breast cancer patients attending public hospitals were recruited in the study.

5.4.5 Sampling frame

All patients diagnosed by histopathology examination (HPE) between 1st January and 31st December 2012 were included. Cases were identified through the hospital registry and Surgery Out-Patient Department (SOPD) or Breast Clinic breast cancer records at each hospital.

5.4.6 Study locations

Six public hospitals in Malaysia. Two hospitals were located in Kuala Lumpur and others in Perak, Johor, Kelantan and Sarawak.

5.4.7 Study period

All breast cancer patients recruited in the study were followed up with a median of 14 months (range: 12 to 18 months) from diagnosis.

5.4.8 Data collection

Data collection was conducted through medical record reviews and followed by interview by using a structured questionnaire that was developed from literature review. The questionnaires were in Malay and English language and were pre-tested for face and content validity amongst breast cancer survivors and breast surgeons to assess whether they met the study objectives. Data between the medical records and patient interviews was cross-validated by the researcher to ensure for accuracy.

5.4.8.1 Medical records review

Data obtained through the records review were the socio-demographic characteristics, medical and family history, treatment adherence and the dates of all important time points (e.g. symptom duration, date of primary care visit, date of diagnostic resolution, date of start treatment).

5.4.8.2 Interview

Data obtained through the interview session were socio-demographic characteristics, medical and family history, treatment adherence and the use of complementary and alternative medicine (CAM). Questions asked on CAM were the use of CAM before treatment, type of CAM used, time of CAM used, the number of CAM used and cost of CAM used.

5.4.9 Conceptual and operational definitions

5.4.9.1 Newly diagnosed breast cancer

All new cases diagnosed with breast cancer by histopathology examination (HPE) regardless of the place of diagnosis. If cases have been referred from other healthcare facilities, details of diagnosis will be traced back from referral letter or medical records.

5.4.9.2 Presentation interval

The interval is defined as the time taken from the symptom discovery to the first presentation at a primary care facility. Presentation delay is defined if there is more than 3 months duration (Lim et al., 2015; Facione & Facione, 2006; Ghazali et al., 2013; Harirchi et al., 2005; Norsa'adah et al., 2011; Unger-Saldaña & Infante-Castañeda, 2009; Montazeri et al., 2003).

5.4.9.3 Diagnosis interval

The interval is defined as the time taken from first presentation at a primary care facility to diagnostic resolution. Diagnosis delay is defined if there is more than 1 month (30 days) duration (Bairati et al., 2007; Ermiah et al., 2012; Huo et al., 2014; Plotogea et al., 2014; Pruitt et al., 2014; Samphao et al., 2009).

5.4.9.4 Treatment interval

The interval is defined as the time taken from the diagnostic resolution to initiation of treatment. Treatment delay is defined if there is more than 1 month (30 days) duration (Caplan et al., 2000; Pack & Gallo, 1938; Pérez et al., 2008; Rastad et al., 2012; Sainsbury et al., 1999; Shandiz et al., 2012).

5.4.9.5 Complementary and alternative medicine (CAM)

CAM is defined as any therapy using methods and products not included in the conventional allopathic medicine (e.g. biologically based practice, mind-body medicines, whole medical system, energy medicines, manipulative and body-based practice) (Farooqui et al., 2015) before commencement of treatments.

5.4.10 Informed Consent

Informed consent is the subject agreement to take part voluntarily in the study. Consent was retrieved after patients were informed and understood the aim of the study, which is prior to data collection. In this study, patients were informed about the research purposes, interview procedures and the rights to willingly consent or refuse to participate in the study. They can withdraw participation at any time of the interview and were assured that there were no possibilities of risks or costs encountered. Confidentiality was also assured during data processing and when reporting or publishing the study.

5.4.11 Data Analysis

All analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago). Continuous data were described by median (range) whereas categorical data were described by frequencies (percentage, %). CAM use and delays in breast cancer were divided into dichotomous outcome; "Non-CAM user" or "CAM user" and "Non-delay" or "Delay".

Univariable logistic regression was conducted to look at the strength of the association between factor of interest (e.g. CAM use) and outcomes (e.g. presentation delay, diagnosis delay and treatment delay). Results were presented as crude odds ratios (OR), 95% confidence interval (CI) and p value <0.05 was considered as significant.

Multivariable logistic regression was used to identify the association between CAM use and delays in presentation, diagnosis and treatment. Variables included in the model were CAM use, age, ethnicity, education level, marital status, household income, employment status, family history with breast cancer, breast lump, symptom interpretation, surgical services and oncology services. Results were presented as adjusted odds ratio (OR), 95% confidence interval (95% CI) with a significant *p* value <0.05.

5.4.12 Operational definitions

There were two types of variables; independent variables and dependent variables. The independent variables encompass the variables that are operated by the researcher (e.g. complementary and alternative medicine (CAM) use). Meanwhile dependent variables are the responses measured in the study (e.g. presentation delay, diagnosis delay, treatment delay). All variables that were used in this study based on their operational definition.

5.5 Results

5.5.1 Use of complementary and alternative medicine (CAM) by patients

Table 5.1 shows the distribution of patients according to complementary and alternative medicine (CAM) use. Results showed 158 (46.5%) of the breast cancer patients had used CAM while 182 (53.5%) did not use CAM. Among the 158 CAM users, 84 (24.7%) of the patients started using CAM after symptom discovery and 74 (21.8%) of the patients started using CAM after confirmation of diagnosis. None of the patients started using CAM after treatments. More than half of the CAM users 108 (68.4%) were reported to use two or more types of CAM. The median number of CAM therapies used by the patients were 4 and ranged from 1 to 32 therapies along the study period. The median cost for CAM was RM500 (~USD 112.40) with minimum of RM50 and maximum of RM12 000.

Table 5.1: Uses of complementary and alternative medicine (CAM) by patients.

CAM user	N	n (%)
Yes	340	158 (46.5)
No		182 (53.5)
Started using CAM		
After symptom discovery	158	84 (53.2)
After diagnosis		74 (46.8)
Number of CAM type		
1 type	158	50 (31.6)
≥ 2 types		108 (68.4)
Number of CAM therapies		
Median (Range)	4 (1 to 32)	
Cost (RM)		
Median (Range)	RM500 (RM50 to RM12 000)	

5.5.2 Types of complementary and alternative medicines (CAM) used by breast cancer patients

Table 5.2 shows the type of CAM used was divided into 5 categories; biological based practices, mind-body medicines, whole medical system, energy medicines and manipulative and body-based therapies. Results show that biological based practices (n=120, 75.9%) was the most frequent type of CAM used by the breast cancer patients with the majority consumed nutritional supplements (n=108). It was followed by the mind-body medicine and whole medical system with 38.6% and 35.4% respectively. Only 5 (3.2%) patients reported using energy medicine while 3 (1.9%) patients underwent massages as their therapy. The types of CAM used by the patients are summarized in the table below.

Table 5.2: Types of CAM used by the breast cancer patients (n=158)

Types of CAM	Cases (n)	n (%)
Biological based practices		
Nutritional supplements (multivitamin)	108	120 (75.9)
Special diet (herbs, juices)	12	
Mind-body medicines		
Prayers	53	61 (38.6)
Others (meditation, tai chi, yoga, qigong)	8	
Whole medical system		
Traditional Chinese medicine	38	56 (35.4)
Cupping	10	
Homeopathy	5	
Ayurveda	3	
Energy medicines		
Ozone therapy	5	5 (3.2)
Manipulative and body-based therapies		
Massage	3	3 (1.9)

*Total percentage may not be 100% due to the choice given for multiple responses.

5.5.3 Demographic and characteristic of non-CAM and CAM user among the breast cancer patients

Table 5.3 below summarizes the demographic and characteristics of CAM users and non-CAM users. Out of 340 patients, 158 (46.5%) were reported as CAM users. CAM use was seen mainly amongst the Malays, low educational status, has family history of breast cancer, those who did not interpret symptom as cancerous, higher cancer stage and non-adherence. CAM use was used in the 6 hospitals ranging from 42% to 75% of the patients in each hospital.

In univariate logistic regression, patients in Kelantan, Malays and those who had not interpreted symptom as cancerous were found to be significant factors associated CAM users. However, after adjustment with other covariates by using multivariate logistic regression, only Malays ethnicity and interpreting symptom as non-cancerous are found independently associated with CAM use.

The odds of CAM use among Malays were 3.32 times higher (OR 3.32; 95% CI: 1.85, 5.97) than the Chinese. Meanwhile, the odds of CAM use among patients who did not interpret symptom as cancerous were 1.79 times higher (OR 1.79; 95% CI: 1.10, 2.92) than those who had interpreted symptom as cancerous. Study locations were not significant after adjustment with other covariates.

The age, study locations, education level, marital status, monthly household income, employment status, family history, breast symptoms, cancer stage and treatment adherence is not associated with CAM use among breast cancer patients in Malaysia.

Table 5.3: Characteristic of Non CAM and CAM user among the breast cancer patients (N=340)

Characteristic	Non-CAM user (n=182)	CAM user (n= 158)	Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
Age						
Median (range)	53 (25, 74)	53 (23,73)	0.98 (0.96, 1.08)	0.232	0.99 (0.97, 1.01)	0.613
Study locations						
Kuala Lumpur (1)	56 (56.0)	44 (44.0)	1.00	-	1.00	-
Kuala Lumpur (2)	43 (53.8)	37 (46.3)	1.09 (0.60, 1.97)	0.763	0.86 (0.43, 1.72)	0.672
Ipoh	28 (58.3)	20 (41.7)	0.90 (0.45, 1.82)	0.789	0.79 (0.37, 1.69)	0.544
Johor Bahru	26 (52.0)	24 (48.0)	1.17 (0.59, 2.32)	0.643	0.79 (0.35, 1.79)	0.586
Kota Bharu	5 (25.0)	15 (75.0)	3.81 (1.28, 11.31)	**0.016**	2.24 (0.64, 7.76)	0.203
Kuching	24 (57.1)	18 (42.9)	0.95 (0.46, 1.97)	0.900	1.06 (0.43, 2.62)	0.884
Ethnicity						
Chinese	71 (68.3)	33 (31.7)	1.00	-	1.00	-
Malay	62 (40.3)	92 (59.7)	3.19 (1.89, 5.39)	**<0.001**	3.32 (1.85, 5.97)	**<0.001**
Indian	32 (59.3)	22 (40.7)	1.47 (0.74, 2.92)	0.261	1.37 (0.64, 2.93)	0.409
Others	17 (60.7)	11 (39.3)	1.39 (0.58, 3.30)	0.453	1.38 (0.53, 3.58)	0.499
Educational level						
Tertiary	25 (51.0)	24 (49.0)	1.00	-	1.00	-
Secondary	141 (54.7)	117 (45.3)	0.86 (0.46, 1.59)	0.640	0.92 (0.46, 1.85)	0.827
Primary	16 (48.5)	17 (51.5)	1.10 (0.45, 2.67)	0.822	1.26 (0.44, 3.59)	0.663

Marital status						
Married	140 (54.1)	119 (45.9)	1.00	-	1.00	-
Single	42 (51.9)	39 (48.1)	1.09 (0.66, 1.80)	0.729	1.09 (0.58, 2.06)	0.729

'Table 5.3, continued'

Characteristic	Non-CAM user (n=182)	CAM user (n= 158)	Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
Household income	129 (52.9)	115 (47.1)	1.00	-	1.00	-
≤RM3000	53 (55.2)	43 (44.8)	0.91 (0.56, 1.46)	0.697	1.13 (0.65, 1.96)	0.654
>RM3000						
Employment status	55 (50.5)	54 (49.5)	1.00	-	1.00	-
Employed	127 (55.0)	104 (45.0)	0.83 (0.52, 1.31)	0.436	0.99 (0.58, 1.68)	0.970
Unemployed						
Family history with breast cancer						
Yes	27 (43.5)	35 (56.5)	1.00	-	1.00	-
No	155 (55.8)	123 (44.2)	0.61 (0.35, 1.06)	0.083	0.57 (0.31, 1.05)	0.072
Breast lump						
Yes	158 (52.7)	142 (47.3)	1.00	-	1.00	-
No	24 (60.0)	16 (40.0)	0.74 (0.37, 1.45)	0.384	0.63 (0.30, 1.32)	0.229

Interpret symptom as cancer	124 (57.7)	91 (42.3)	1.00	-	1.00	-
Yes	58 (46.4)	67 (53.6)	1.57 (1.01, 2.45)	**0.045**	1.79 (1.10, 2.92)	**0.018**
No						

'Table 5.3, continued'

Characteristic	Non-CAM user (n=182)	CAM user (n= 158)	Crude Odd Ratio (95% CI)	P value[a]	Adjusted Odd Ratio (95% CI)	P value[b]
Stage at diagnosis						
Stage I	33 (55.9)	26 (44.1)	1.00	-	1.00	-
Stage II	74 (57.8)	54 (42.2)	0.92 (0.49, 1.72)	0.809	0.79 (0.39, 1.58)	0.509
Stage III	58 (50.9)	56 (49.1)	1.22 (0.65, 2.30)	0.528	1.04 (0.50, 2.15)	0.910
Stage IV	17 (43.6)	22 (56.4)	1.64 (0.72, 3.71)	0.233	1.30 (0.52, 3.21)	0.565
Initial treatment						
Adherence	155 (54.8)	128 (45.2)	1.00	-	1.00	-
Non-adherence	27 (47.4)	30 (52.6)	1.33 (0.76, 2.38)	0.308	1.34 (0.76, 2.38)	0.308

[a]Univariable Logistic Regression, [b]Multivariable Logistic Regression
Significant value p<0.05

5.5.4 Complementary and alternative medicine (CAM) use and delays in breast cancer

Table 5.4 shows the association between CAM use and delays in presentation, diagnosis and treatment in breast cancer. From the analysis, it is found that CAM use is associated with delays in presentation (OR 1.65; 95% CI: 1.05, 2.59), diagnosis (OR 2.42; 95% CI: 1.56, 3.77) and treatment (OR 1.74; 95% CI: 1.11, 2.72).

However, after adjustment with other covariates (refer table 5.5), CAM use is only associated with delays in presentation (OR 1.71; 95% CI: 1.05, 2.78) and diagnosis (OR 2.58; 95% CI: 1.59, 4.17) but not for treatment (OR 1.58; 95% CI: 0.98, 2.55). Findings indicate that CAM users were 1.71 times higher odds to delay presentation and 2.58 times higher odds to delay diagnosis compared to non-CAM users. Besides that, symptoms without breast lumps (OR 2.17; 95% CI: 1.06, 4.42) and surgical biopsy (OR 2.32; 95% CI: 1.23, 4.37) were also the independent factors for diagnosis delay, while not having a family history of breast cancer (OR 1.81; 95% CI: 1.01, 3.26) was the independent factor for treatment delay.

Table 5.4: Univariate analysis of association between CAM use and delays in presentation, diagnosis and treatment among the breast cancer patients (N=340)

Characteristic	Presentation delay		Diagnosis delay		Treatment delay	
	Crude OR (95% CI)	P value	Crude OR (95% CI)	P value	Crude OR (95% CI)	P value
CAM						
Non-user	1.00	-	1.00	-	1.00	-
User	**1.65 (1.05, 2.59)**	0.028	**2.42 (1.56, 3.77)**	<0.001	**1.74 (1.11, 2.72)**	0.015

Univariable Logistic Regression, Significant value p<0.05

Table 5.5: Multivariate analysis of association between CAM use and other characteristics with delays in presentation, diagnosis and treatment among the breast cancer patients (N=340)

Characteristic	Delay in presentation (n=119)		Delay in diagnosis (n=142)		Delay in treatment (n=120)	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
CAM						
Non-user	1.00	-	1.00	-	1.00	-
User	**1.71 (1.05, 2.78)**	0.029	**2.58 (1.59, 4.17)**	<0.001	1.58 (0.98, 2.55)	0.058
Age						
≤50 years	1.00	-	1.00	-	1.00	-
>50 years	0.65 (0.39, 1.09)	0.110	1.21 (0.72, 2.02)	0.470	1.02 (0.61, 1.71)	0.919
Ethnicity						
Chinese	1.00	-	1.00	-	1.00	-
Malay	1.24 (0.70, 2.18)	0.449	0.90 (0.51, 1.57)	0.711	1.53 (0.86, 2.70)	0.142
Indian	0.69 (0.32, 1.48)	0.343	1.13 (0.55, 2.33)	0.721	1.69 (0.80, 3.56)	0.164
Others	0.81 (0.31, 2.11)	0.664	0.51 (0.18, 1.41)	0.199	0.95 (0.35, 2.54)	0.922
Educational level						
Tertiary	1.00	-	1.00	-	1.00	-
Secondary	1.75 (0.82, 3.72)	0.148	0.98 (0.48, 1.98)	0.959	1.03 (0.50, 2.11)	0.928
Primary	1.88 (0.64, 5.50)	0.250	2.01 (0.71, 5.65)	0.185	1.92 (0.69, 5.34)	0.209
Marital status						
Married	1.00	-	1.00	-	1.00	-

Single	1.51 (0.86, 2.65)	0.146	1.27 (0.73, 2.22)	0.387	0.76 (0.43, 1.34)	0.354

‘Table 5.5, continued’

Characteristic	Delay in presentation (n=119)		Delay in diagnosis (n=142)		Delay in treatment (n=120)	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Household income						
≤RM3000	1.00	-	1.00	-	1.00	-
>RM3000	1.56 (0.93, 2.63)	0.090	0.64 (0.37, 1.10)	0.108	1.07 (0.59, 1.70)	0.979
Employment						
Employed	1.00	-	1.00	-	1.00	-
Unemployed	1.62 (0.93, 2.82)	0.088	0.68 (0.40, 1.17)	0.174	0.88 (0.51, 1.51)	0.648
Family history with breast cancer						
Yes	1.00	-	1.00	-	1.00	-
No	1.65 (0.86, 3.17)	0.126	0.80 (0.44, 1.47)	0.486	**1.81 (1.01, 3.26)**	0.049
Breast lump						
Yes	1.00	-	1.00	-	-Nil-	
No	0.94 (0.45, 1.94)	0.869	**2.17 (1.06, 4.42)**	0.033		
Interpret symptom as cancer						

Yes	1.00	-	1.00	-	-Nil-	
No	0.77 (0.47, 1.27)	0.316	0.91 (0.56, 1.49)	0.734		

‘Table 5.5, continued’

Characteristic	Delay in presentation (n=119)		Delay in diagnosis (n=142)		Delay in treatment (n=120)	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Type of biopsy						
Needle	-Nil-		1.00	-	-Nil-	
Surgical			**2.32 (1.23, 4.37)**	0.009		
Surgical services						
Breast surgeon	-Nil-		-Nil-		1.00	-
General surgeon					1.50 (0.91, 2.48)	0.111
Oncology services						
Available	-Nil-		-Nil-		1.00	-
Not available					0.88 (0.48, 1.62)	0.694

Multivariable Logistic Regression, Significant value p<0.05, Nil = Not included

5.6 Discussion

Findings of this study showed that CAM use was prevalent among the breast cancer patients in all of 6 public hospitals. However, the rate of 46.5% was lower than 51-88.3% of CAM use reported in other Malaysian studies (Chui et al., 2014; Chui et al., 2015; Knight et al., 2015; Norsa'adah et al., 2011; Raja et al., 2013; Saibul et al., 2012; Taib et al., 2007). The lower prevalence could be due to differences in study instruments, sample used and time point of the CAM use (Helyer et al., 2006; Yew et al., 2015).

Studies on CAM use among breast cancer patients has found that CAM use was influenced by demographic, lifestyle and clinical factors (Richardson et al., 2000). In this study and similar to many local studies, ethnicity was found to be associated with CAM use where the Malays were observed to use CAM more than other ethnics groups (Knight et al., 2015; Saibul et al., 2012). Although some studies in Malaysia reported that there was no significant association between ethnicity and CAM, Malays were found to be the highest CAM user compared to Chinese and Indian (Chui et al., 2014; Farooqui et al., 2015; Hamidah et al., 2009; Raja et al., 2013). Malays are dominated by strong community relationships where family and friends involvement greatly influence the patients' treatment-seeking behaviour (Muhamad et al., 2012) which indirectly leads to CAM use. Studies in Malaysia and Singapore have found that Malay ethnicity was an independent factor of overall survival in breast cancer patients after adjustment for stage at presentation and type of treatments (Nirmala et al., 2012; Taib et al., 2011). It is plausible that use of CAM may be a factor affecting the prognosis of Malay patients, and this should be investigated further. In addition, CAM is easily available, affordable and widely advertised causing high utilization, illustrates that CAM is highly accepted practice in the local Malaysian cultures but there is lack of control on its' use.

Besides that, we also observed in this study that by not interpreting symptom as cancerous was significantly associated with CAM use. This highlights the importance of symptom appraisal as reported in other studies (Bish et al., 2005; Martins et al., 2013; Taib et al., 2011). Appraisal is defined as a decision making process (Andersen et al., 1995) which begins when the patients discovered an abnormality in their breasts (Abdullah et al., 2013). Results in this study showed that the patients' interpretation on symptoms as non-cancerous was a significant factor in CAM use. This illustrates that the symptom interpretation among the Malaysian breast cancer patients is poor either with or without symptom of lump as seen in other studies (Bish et al., 2005; Burgess et al., 1998; Taib et al., 2011). Lack of knowledge about the correct interpretation of symptoms causes patients to have difficulty to present or decide in seeking medical attention and we are particularly concerned that CAM was used for perceived benign conditions of the breast.

Hence, the socio-cultural influence on health behaviour of Malay patients in the use of CAM as an initial help-seeking strategy for breast symptoms is compounded further by poor literacy in breast cancer symptoms could lead to delays. This demands an urgent call to provide culturally appropriate public health education on breast cancer symptoms and help-seeking strategies to this group of women. Studies showed that they were influenced by family members and friends, thought that CAM works, had bad experience in hospital, financial problems, was afraid of loss of employment after the mastectomy, time restraint, having young children, embarrassed to see doctors, used as the last resort, ease of availability and affordability were the reasons for using CAM (Abdullah et al., 2013; Taib et al., 2007).

Poor symptom recognition by healthcare providers may compound this further (Lim et al., 2015; Taib et al., 2011). Findings from a study with a mixture of government and private hospitals showed timely cancer surgical services but lower achievement for

radiotherapy and services (Lim et al., 2014). Public hospitals in Malaysia provide almost free or highly subsidised healthcare and produces excellent maternal and child healthcare outcomes, however little is known on the efficiency in cancer care as there is no national audit on diagnostic time for cancers in Malaysia.

Findings from this study showed that CAM use was significantly associated with delayed presentation among breast cancer patients in Malaysia. Poor knowledge about the correct interpretation of symptoms causes patients to have difficulty to decide in seeking medical attention and being exposed to complementary and alternative medicine (CAM) early in on their help-seeking effort (Taib et al., 2014). The interpretation of symptoms related to cancer is influenced by not just social and the cultural context (Andersen et al., 2009) but psychological fears of discovering cancer and their treatments places them in denial and hence avoiding medical attention (Taib et al., 2014). This refusal could be related to a coping mechanisms to reduce pain, anxiety, fear and fatalism towards breast cancer and its' treatments and thus, CAM may be used to control these psychological disturbances. Most patients took CAM as a way to avoid surgery and the perception that traditional medicine is more effective than modern medicine (Norsa'adah et al., 2011) and subsequently present late to hospital after they found that CAM was not effective (Norsa'adah et al., 2012). Since public hospitals in Malaysia are heavily subsidized and readily available to the population (CPR Report, 2009; Lim et al., 2014), CAM use may impact delays in presentation. Therefore, with a background of poor understanding of disease, and other competing issues, CAM use remains as the main player for presentation delay among breast cancer patients in Malaysia.

Similar to presentation delay, diagnosis delay was also associated with complementary and alternative medicine (CAM) use as seen in a local study (Norsa'adah et al., 2011). An early exposure to CAM causes continuation of use up to diagnosis and

treatment. Fear of exposure to mammographic radiation (Al-Naggar & Bobryshev, 2012), fear of diagnostic test (Weinmann et al., 2005), pain during biopsy procedures (Elmore et al., 2011) and fear of diagnosis (Macleod et al., 2009) could lead to CAM use to increase physical and emotional health (Norsa'adah et al., 2012). Therefore, with a background of fear on the diagnostic investigations and other competing issues, CAM use remains as the main player for diagnosis delay among breast cancer patients in Malaysia. Community educational programs concentrating on knowledge of how biopsy is performed and correcting misconceptions would improve the quality of diagnostic and cancer care in Malaysia.

Complementary and alternative medicine (CAM) use was found to be associated with treatment delay in univariate analysis, but no association was found after adjusting with other covariates. Although delay in treatment of breast cancer was not associated with CAM use, many studies reported an association between CAM use and non-adherence to breast cancer treatments (Chui et al., 2014; Chui et al., 2015; Leong et al., 2007; Lim et al., 2014). This suggests that the use of CAM did not interfere with the speed of provision on treatment once the patients have decided on treatments, but have some influence on non-adherence to treatment which is controlled by the patients.

Accessibility to health facilities in Malaysia is not a problem since the nearest health center is within 5km radius from the households (CPR Report, 2009). Public medical care services in Malaysia is subsidized and charges a small fee (Norsa'adah et al., 2012) and was reported that 82% of breast cancer patients could access breast surgery timely (Lim et al., 2014). These suggest that access to health care may not be the factor for delays in presentation, diagnosis, and treatment in Malaysia.

This study highlights that Malaysia has a pluralistic health seeking culture where the conventional and alternative therapies co-exist together in the health system. Since

complementary and alternative medicine (CAM) plays a direct role in delays in presentation and diagnosis, a comprehensive intervention strategy is needed to reduce the reliance of CAM use among patients. The healthcare providers in Malaysia need to explicitly address CAM use in their consultation with patients. Although it is not associated with treatment delays, awareness of its use need to be addressed. In addition, linguistic and culturally appropriate health education on breast cancer symptoms and the importance of seeking early cancer diagnosis should be provided to the targeted group to improve the breast health literacy in Malaysia.

5.7 Limitation

The low response rate is due to difficulty in obtaining medical records may have excluded patients who experienced delays in presentation, diagnosis or treatment thus limiting the validity of the study. Moreover, a proportion of the patients were interviewed retrospectively about their CAM use, hence the propensity for recall bias.

Statistically the sampling could not really represent to the Malaysian Breast Cancer patients in general. But since most of the main hospitals in the study location (e.g. Kuala Lumpur, Ipoh, Johor Bahru, Kota Bharu and Kuching) are tertiary hospitals and in different regions of the country, the findings obtained are relevant for the clinicians and the policy makers in the management of the breast cancer and CAM use in Malaysia.

5.8 Strength

To the best of our knowledge, this is the first study to examine the relationship of CAM use and delays in breast cancer among patients attending public hospitals in Malaysia. Every precaution and resources were utilized to obtain record, hence a retrieval rate of 39% in busy public hospitals with limitations in manual record keeping gives a good representation. Furthermore, the study sample comprised of multi-ethnic patients in public hospitals from all regions, thus making it possible to infer the findings to all breast

cancer patients in Malaysia. Linguistic and culturally appropriate health education on breast cancer symptoms and the importance of seeking early cancer diagnosis should target the patients who are likely to use CAM as preferred initial treatments. In addition, the findings support that practice of CAM should be highly regulated and monitored strictly by the authorities to prevent false claims.

5.9 Contribution and Implications of the study

Malaysia has a pluralistic health seeking culture where the conventional and alternative therapies co-exist as evident in this study. Therefore, healthcare providers in Malaysia need to explicitly address complementary and alternative medicine (CAM) in their consultation with patients as CAM plays a direct role in delays in presentation and diagnosis. Although it is not associated with treatment delays, awareness of it's use need to be addressed.

5.10 Conclusion

The prevalence of CAM use among the breast cancer patients was high. Patients from Malay ethnicity and not interpreting symptom as cancerous were significantly associated with CAM use. The use of CAM was significantly associated with delay in presentation and resolution of diagnosis. Difficulty in obtaining all medical records may have excluded patients who experienced delays in presentation, diagnosis or treatment but every precaution and resources were utilized to obtain record. This study suggests further evaluation of access to breast cancer care is needed as poor access may promote the use of CAM. However, since public hospitals in Malaysia are heavily subsidized and readily available to the population, CAM use may impact delays in presentation and diagnosis among breast cancer patients in Malaysia.

5.11 Chapter summary

This chapter has been published in an article entitled “Complementary and alternative medicine (CAM) use and delays in presentation and diagnosis of breast cancer patients in public hospitals in Malaysia” (Mohd Mujar et al., 2017). The prevalence of complementary and alternative medicine (CAM) use was high among the breast cancer patients. CAM plays a direct role in presentation and diagnosis delays of breast cancer patients in Malaysia.

CHAPTER 6: CONCLUSION

6.1 Outline of this chapter

The final chapter summarizes the research findings presented in Chapter 3, 4, and 5, where Chapter 3 and 5 have been published (Mujar et al., 2017; Mujar et al., 2013). This chapter will summarise the study findings and provide recommendations or suggestions arising from the studies as well as the contributions, the implication on policy, practice and future research.

6.2 Study objective

All study objectives have been successfully carried out as follows;

1. The impact of time to primary treatment after a diagnosis of breast cancer and overall survival has been determined.
2. The time intervals between important time points in the breast cancer journey from symptom discovery to initial treatment have been determined.
3. The proportion of delays in presentation, diagnosis and treatment of breast cancer patients has been determined.
4. The factors associated with delays in presentation, diagnosis and treatments of breast cancer patients have been determined.
5. The factors associated with non-adherence to breast cancer treatments (e.g. surgery, oncology therapy) amongst breast cancer patients have been determined.
6. The associated factors of CAM use amongst breast cancer patients and its relationship with delays in presentation, diagnosis and treatments of breast cancer has been determined.

6.3 Summary of all research findings, conclusions and recommendation

6.3.1 Impact of delay on overall survival

Delays to breast cancer treatment have no impact on overall survival. Findings show that survival is not related to delay but with the stage at diagnosis, which is a modifiable prognostic factor. Therefore, the strategies to present at early stages would be to reduce delay in presentation, diagnosis, and treatment. These strategies may improve survival. Hence, the urgency is to modify stage. Undoubtedly a larger prospective study with clearly defined time points from symptom discovery until treatment completion is needed to measure the impact of delays on breast cancer survival. The effect on time may be mixed because of the heterogeneity of cancer biology where some types of tumor are more aggressive than others. This may explain why delay was not found to have any independent association to outcomes. Those with higher grade tumor, estrogen and progesterone receptor negative or Her2 overexpressed tumor are more aggressive at diagnosis. Besides these factors, we lack predictive models to accurately identify which patients are afflicted with aggressive type of cancer, emphasizes why patients should not delay. Hence, drawing up meaningful quality indicators to breast cancer care in Malaysia may also need to be done base on experts' opinions rather than solely on the evidence.

6.3.2 Presentation delay

Presentation delay begins from the symptom discovery until presentation to the primary health care facility. Locality and complementary and alternative medicine (CAM) use were the independent factors for presentation delay, suggesting strong influence of socio-culture and poor breast health literacy among patients in Malaysia. We suggest that delayed presentation can be improved by reducing ‘Presentation Interval’ where the patients identify symptoms and seek help from primary health care facilities much earlier. Hence, there is an urgent demand to provide culturally appropriate public

health educational programs, concentrating on knowledge of how to get diagnosed and receiving treatments. An update of the 'Breast-Self Examination' guideline is needed to increase the breast cancer awareness and adopt positive help-seeking strategies. Therefore, intervention strategies need to be practiced in the community to decrease presentation delay and downstage breast cancer in Malaysia.

6.3.3 Diagnosis delay

Diagnosis delay begins from presentation at the primary health care facility to the resolution of a diagnosis which includes the referral, biopsy, report and disclosure time intervals. The use of CAM, symptom without lump, surgical biopsy and undergoing two or more biopsies were the independent factors for diagnosis delay suggesting patient and health system challenges, CAM use, lack of competence, and expedited workflows among healthcare providers in Malaysia were seen. Symptom without lump may suggest the need for image guided biopsies that may not be accessible in a timely manner, and the repeated biopsies may give clues to non-existent standard operating procedures of multiple inconclusive biopsies before conclusive excision biopsy is done. These factors suggest the challenges of producing timely histopathology diagnostic procedures and operating lists. Patients referred from within same hospital departments i.e. out-patient department (OPD) to diagnostic surgical clinics had longer diagnosis resolution than those from private clinics (GP), may suggest lack of navigation system within the same hospital. We suggest that delayed diagnosis can be improved by reducing 'Referral Interval' where the healthcare provider may actually identify and refer patients to the diagnostic centre much earlier. Competency in clinical breast-examination (CBE) and clinical skills of healthcare providers play a role in identify, refer and diagnose early as well as an updated of referral guidelines could avoid diagnosis delay, thus improve the quality of breast cancer care in Malaysia.

6.3.4 Treatment delay

Treatment delay begins from a diagnosis resolution to an initiation of treatment. Geographic locality and those diagnosed at other hospitals were the independent factors for treatment delay suggesting strong influence of socio-culture among patients on treatment decisions in different locations in Malaysia as well as the variability of the standards of care in different locations. This may be due to the lack of standard operating procedures in navigating patients from diagnostic centre to treatment facilities. Lack of breast surgeon or oncologist in public hospitals in Malaysia did not predict treatment delay suggest challenges in cross-referral between the hospital departments even within specialist hospitals may have led to prolongation of treatment interval. We suggest that delayed treatment can be improved by reducing 'Treatment Interval' where navigation to treatment facilities could be made much earlier through a systematic procedure and collaborative multidisciplinary decision-making approach. Hence, healthcare professionals play an important role in guiding the patients and their family through proper treatment consultation and assist in making early treatment decisions and navigating patients through health systems to avoid delay and thus improve the quality of breast cancer care in Malaysia.

6.3.5 Adherence to breast cancer treatments

There was high accessibility of surgery at public hospitals in Malaysia. Locality and those requiring mastectomy (MAC) were the independent factors for non-adherence to surgery possibility due to strong influence of socio-cultural factors and possibly body image issues among patients in different parts of Malaysia. We also found high rates of non-adherence to radiotherapy, chemotherapy and hormone therapy. Location of hospital whereby patients from Ipoh, Perak was an independent factor for non-adherence to oncology therapy may be due to lack of oncology services in the same hospital. Lack of breast surgeon or oncologist in public hospitals in Malaysia did not predict non-adherence

to surgery or oncology therapy may suggests that despite having more specialised care, other supportive care e.g. emotional and psychological support are not available in specialist hospitals. We propose that non-adherence to surgery and oncology therapy can be improved by offering supportive care support to all cancer patients. Comprehensive communication and detailed information when counseling patients for treatment options as well as emotional support by the healthcare professionals may help to increase adherence rate, thus improve the quality of cancer care in Malaysia.

6.3.6 Complementary and alternative medicine (CAM) use

There was high complementary and alternative medicine (CAM) use which was associated with delays in presentation and diagnosis of breast cancer in Malaysia. Malays and patients who not interpreting symptom as cancerous were the independent factors for CAM use indicate that the socio-cultural influence on health behavior of Malay women on the use of CAM as an initial help-seeking strategy for breast symptoms was compounded further by poor literacy in breast cancer symptoms. Healthcare providers should counsel about CAM use at presentation in the primary care facility and at the diagnostic centre to avoid delays in presentation and diagnosis. We suggest that CAM use can be decreased by providing culturally appropriate public health education on breast cancer symptoms and help-seeking strategies especially to Malays which can reduce CAM use and improve breast cancer care quality in Malaysia.

6.4 Chapter summary

Although we showed that delays to breast cancer treatment had no impact on overall survival but a strategy for early presentation, diagnosis and treatment of breast cancer remain useful. There was a high rate of delays in presentation, diagnosis and treatment at public hospitals in Malaysia. Factors influencing delays and non-adherence were

multifactorial implicating a complex interaction between variations in geography on influence of socio-culture, patients and health systems in Malaysia. The prevalent use of complementary and alternative medicine (CAM) had impacted delays in presentation and diagnosis of breast cancer.

Mutual collaboration from multiple areas involving patients and multidisciplinary healthcare sectors are important to reduce delays, non-adherence to treatments and CAM use. Therefore, a comprehensive intervention in the community where providing information on symptom recognition, timely diagnosis, improving referral networks within the health systems, timeliness in clinical pathways, and provision of audits to monitor timeliness and outcomes are suggested to improve breast cancer care quality in Malaysia.

For policymakers, these points are measurable for health care performance. Awareness of delays by patients or/and health systems would help in designing interventions, enabling earlier presentation, diagnosis and treatment. Understanding the importance of complementary and alternative medicine (CAM) should guide policymakers to regulate its use in the community and allow some emphasis for it when counseling patients for treatment.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

Publications

1. Mujar, M., Dahlui, M., Yip, C. H., & Taib, N. A. (2013). Delays in time to primary treatment after a diagnosis of breast cancer: Does it impact survival? *Preventive Medicine*, *56*(3–4), 222–224. http://doi.org/10.1016/j.ypmed.2012.12.001

2. Mohd Mujar, N. M., Dahlui, M., Emran, N. A., Hadi, I. A., Yan, Y. W., Arulanantham, S., Chea, C.H., Taib, N. A. (2017). Complementary and alternative medicine (CAM) use and delays in presentation and diagnosis of breast cancer patients in public hospitals in Malaysia. *PLoS ONE*, *12*(4), 1–12. https://doi.org/10.1371/journal.pone.0176394

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1. Mohd Mujar, N. M., Dahlui, M., Emran, N. A., Hadi, I. A., Yan, Y. W., Arulanantham, S., Chea, C.H., Taib, N. A. Presentation, diagnosis and treatment of breast cancer at public hospitals in Malaysia: The time intervals and factors associated with delays and non-adherence.

2. Mohd Mujar, N. M., Dahlui, M., Emran, N. A., Hadi, I. A., Yan, Y. W., Arulanantham, S., Chea, C.H., Taib, N. A. The patients characteristic on presentation, diagnosis and treatment of breast cancer at public hospitals in Malaysia.

Papers presented

1. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Oral presentation. The impact of duration of symptoms and treatment interval on survival among women with breast cancer: Experience from the University Malaya Medical Centre (UMMC), Malaysia. *6th General Assembly of the Asian Pacific Organization for Cancer Prevention.* Kuching, Sarawak. 26th -29th Apr 2012.

2. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Poster presentation. Breast cancer delay in Malaysia. A systematic study by The Breast Chapter, College of Surgeons of Malaysia. *Annual General Meeting & Annual Scientific Meeting by College of Surgeons Academy of Medicine of Malaysia.* Kuantan, Pahang. 25th - 27th May 2012.

3. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Oral presentation. Does time to primary treatment in breast cancer impact survival? *1st Asia Pacific Clinical Epidemiology & Evidence-Based Medicine Conference.* Kuala Lumpur. 6th – 8th July 2012.

4. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Poster presentation. Patient's adherence to surgery for breast cancer among women attending public hospitals in Malaysia. *Annual Scientific Congress of The Malaysian Oncological Society (ASCOMOS).* Kuala Lumpur. 29th-1st Dec 2013.

5. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Oral presentation. Non-adherence to chemotherapy amongst breast cancer patients attending public hospitals in Malaysia. *The 6th International Conference on Postgraduate Education.* Ayer Keroh, Malacca. 17th-18th Dec 2014.

6. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Poster presentation. Adherence to hormonal therapy amongst breast cancer patients attending public hospitals in Malaysia. *Annual General Meeting & Annual Scientific Meeting by College of Surgeons Academy of Medicine of Malaysia (CSAMM).* Penang. 29th-31st May 2015.

7. Mujar NM, Maznah D, Aina EN, Imisairi AH, Yan YW, Sarojah A, Chea CH, Taib NA. Oral presentation. The rate and factors associated with non-adherence to surgery, chemotherapy, radiotherapy and hormonal therapy among breast cancer patients attending public hospitals in Malaysia. *Annual Scientific Congress of the Malaysian Oncological Society (ASCOMOS)*, 8-10 Dec 2017, Pullman Hotel, Kuching Sarawak.

Achievements

1. Best Poster Presentation at Annual Scientific Congress of the Malaysian Oncological Society (ASCOMOS), 29-1 Dec 2013, Shangri-La Hotel, Kuala Lumpur.

2. Best Poster Presentation at Annual General Meeting & Annual Scientific Meeting by College of Surgeons Academy of Medicine of Malaysia. (CSAMM), 29th-31st May 2015, G Hotel, Pulau Pinang.

3. Best Oral Presentation at Annual Scientific Congress of the Malaysian Oncological Society (ASCOMOS), 8-10 Dec 2017, Pullman Hotel, Kuching Sarawak.