BREAST CONSERVING THERAPY VERSUS MASTECTOMY IN YOUNG BREAST CANCER PATIENTS IN ASIAN SETTINGS

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FACULTY OF MEDICINE
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ABSTRACT

Several studies in Asia point towards high mastectomy rates among patients with early stage breast cancer. In the current study, we assessed the surgical trends in young Asian women with early breast cancer, and compared overall survival (OS) following breast conserving therapy (BCT) versus mastectomy in these patients. Patients aged <50 years diagnosed with stage I or stage II breast cancer between 1990 and 2012 in four hospitals in Malaysia, Singapore and Hong Kong were included (N=3536). Logistic regression analyses were performed to determine the demographic and clinical factors associated with type of surgery. Through a Cox regression analysis, mortality in patients subjected to BCT were compared to those receiving mastectomy, while adjusting for possible confounders using propensity score method. Most patients received mastectomy (63.5%). Over 15 years, rates of BCT increased substantially in Singapore, whereas only a modest increase was observed in Malaysia, and no change in trend was observed in Hong Kong. BCT was significantly associated with Malay ethnicity, smaller tumours, no lymph node involvement, low grade tumours, hormonal receptor positivity, lack of HER2 expression, and no adjuvant chemotherapy. Nevertheless, survival was not significantly different between women receiving BCT and mastectomy; 5-year OS; 94.9% (95%CI 93.5 to 96.3) and 92.9% (95%CI 91.7 to 94.1), respectively; the 10-year OS; 87.0% (95% CI, 84.5-89.6) and 84.8% (95% CI, 84.6 – 85.0), respectively. The adjusted hazard ratio comparing BCT versus mastectomy was 0.82 (95%CI, 0.64-1.04), showing no significant differences in survival between the two surgical groups. Subgroup analyses by country and ethnicity did not change the main inference. Findings from this study will be useful in facilitating surgical decision-making in young Asian breast cancer patients. As there appears to be no significant survival difference between patients undergoing BCT and mastectomy,

eligible young breast cancer patients in Asian settings should be counseled to opt for BCT, which is less disfiguring.

ABSTRAK

Kanser payudara adalah penyebab utama kematian akibat kanser di seluruh dunia. Kajian baru-baru ini menunjukkan kadar mastektomi lebih tinggi di kalangan pesakit kanser payudara peringkat awal di Asia, yang mungkin disebabkan oleh persepsi terhadap hasil jangka hayat yang lebih baik dengan mastektomi dan ketakutan. Dalam kajian semasa, kami menilai hasil jangka hayat (OS) mereka yang mangalami kanser payudara peringkat awal yang dirawat dengan terapi pemuliharaan payudara (BCT) berbandingkan mastektomi di Asia. Pesakit yang berusia <50 tahun yang dikenal pasti menghidap penyakit kanser payudara di empat buah hospital di Malaysia, Singapura dan Hong Kong dari 1990-2012 digunakan (n = 3536). Analisis regresi logistik telah digunakan untuk menentukan faktor-faktor demografi dan klinikal yang berkaitan dengan jenis pembedahan. Kelangsungan hidup secara keseluruhan dianggarkan menggunakan analisis Kaplan-Meier. Skor Kecenderungan (PS) digunakan untuk mengimbangi demografi, tumor dan ciri-ciri rawatan yang telah dibahagikan secara tidak sama rata antara kumpulan "BCT" dan "mastektomi". Seterusnya, model regresi Cox yang diselaraskan untuk PS pesakit telah digunakan untuk menganggarkan kesan jenis pembedahan pada kelangsungan hidup secara keseluruhan. Majoriti pesakit muda dengan kanser payudara peringkat I dan II menerima mastektomi (63.5%). Walaupun kadar terapi pemuliharaan payu dara (BCT) meningkat dengan ketara di Singapura, hanya peningkatan sederhana diperhatikan di Malaysia, manakala tiada perubahan dalam kadar BCT diperhatikan di Hong Kong sepanjang 15 tahun. Terapi pemuliharaan payu dara (BCT) dikaitkan secara signifikan dengan etnik melayu, tumor yang lebih kecil, tidak penglibatan nodus limfa, tumor gred rendah, hormon reseptor positif, kekurangan ekspresi HER2, dan tidak ada kemoterapi yang membantu. Walau bagaimanapun, kelangsungan hidup tidak jauh berbeza antara wanita yang menerima terapi pemuliharaan payu dara (BCT) dan mastektomi; OS 5 tahun; 94.9% (95% CI 93.5

hingga 96.3) dan 92.9% (95% CI 91.7 hingga 94.1); OS 10 tahun; 87.0% (95% CI, 84.5-89.6) dan 84.8% (95% CI, 84.6 - 85.0). HR yang membandingkan terapi pemuliharaan payu dara (BCT) dengan mastektomi berikutan pelarasan untuk skor kecenderungan adalah adalah 0.82 (95% CI, 0.64-1.04), tidak menunjukkan perbezaan yang signifikan dalam jangka hayat antara kedua-dua jenis pembedahan. Analisis sub kumpulan mengikut negara dan etnik tidak mengubah kesimpulan utama. Penemuan dari kajian ini akan berguna dalam memudahkan proses membuat keputusan dalam pembedahan di kalangan pesakit kanser payudara yang muda di Asia. Memandangkan tidak terdapat perbezaan ketara dalam kelangsungan hidup keseluruhan di antara pesakit kanser payudara yang menjalani terapi pemuliharaan payu dara (BCT) dan mastektomi, oleh yang demikian pesakit kanser payudara muda yang layak di persekitaran Asia patut diberi nasihat untuk memilih terapi pemuliharaan payu dara (BCT), yang memberi hasil yang memuaskan di kalangan wanita muda.

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Author

Siamala Sinnadurai

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LIST OF SYMBOLS AND ABBREVIATIONS

OS	:	Overall Survival
CI	:	Confidence Interval
BC	:	Horseradish peroxidase
BCT	:	Breast Conserving Therapy
ER	:	Estrogen Receptor
PR	:	Progesterone Receptor
Her2/neu	:	Human Epidermal Growth Factor Receptor 2
UMMC	:	University Malaya Medical Centre
AJCC	:	American Joint Committee on Cancer
LVI	:	Lymphovascular Invasion
TNM	:	Classification of Malignant Tumours
OR	:	Odds Ratio
HR	:	Hazard Ratio
PS	:	Propensity Score
SPSS	:	Statistical Package for the Social Science
IBM	:	International Business Machines
RT	:	Radiotherapy/Radiation therapy

CHAPTER 1: INTRODUCTION

1.1 Background of the study

Breast carcinoma is the most typically diagnosed malignance among women and known as second major cause of cancer death worldwide, which contributing to 11.9% (nearly 1.7 million) of the total number of new cases (Organization, 2014). While, breast cancer incidence rates reported high in more developed countries, the trend in global incidence has been changing over the last two decades whereby in 2008, the reported new cases in less developed countries almost reached the numbers reported in more developed countries (Youlden, Cramb, Yip, & Baade, 2014). By 2012, the majority (53%) of the new breast cancer cases were mostly from less developed regions such as Asia and it is expected that the number of cases will be increasing over time (Youlden et al., 2014). The constant rise in breast cancer incidence in Asia has become a crucial public health concern.

Recent studies reported that, the proportion of young women or premenopausal young women diagnosed with breast cancer is substantially greater in less developed and developing region like Asia (Ghiasvand, Adami, Harirchi, Akrami, & Zendehdel, 2014). Followed by another finding using Singapore-Malaysia database by Bhoopathy et al reported that, nearly 50% of Asian female detected with breast carcinoma before the age of 50 years old (Nirmala Bhoo-Pathy et al., 2012) compared to developed region, wherein breast cancer among women younger than 50 years old accounts for about 23% of the total (Smigal et al., 2006). It does reflect that, there are huge numbers of young breast

cancer patients in Asia, which need take into account. Although breast cancer is a relatively rare disease among young women compared with older women, a diagnosis with breast cancer will substantially impact the young patient's life as well as her family and society as a whole.

It was revealed that breast cancer in younger female patients is associated with important clinical problems (Winchester, Osteen, & Menck, 1996). Breast carcinoma in young cancer survivors seems to be a more aggressive disease compared to their older patients. Due to, breast carcinoma occurring in younger women usually in relation with a higher percentages of pathological features with more aggressive diseases such as greater numbers of late stage at diagnosis, involvement of lymph nodes, high tumour histological grade, with presence of lymphatic or vascular invasion, extensive intraductal component, lack of estrogen and progesterone receptor, over expression of Her2 neu gene and higher S-phase fraction and to have lower 5 year survival compared to their older counterpart (Albain, Allred, & Clark, 1993; Nixon et al. (1994); Winchester et al., 1996) (Braithwaite et al., 2010; Wildiers et al., 2007). Several other studies also have revealed that young women with breast cancer tend to have high rates of local recurrence (Adri C Voogd et al., 2001), contralateral breast cancer (Rubino, Arriagada, Delaloge, & Lê, 2010), high mortality rate (Ankit Bharat, Rebecca L Aft, Feng Gao, & Julie A Margenthaler, 2009), high proportion of triple-negative cancers (Collins et al., 2012), and with lower survival (Bastiaannet et al., 2010) mostly leading to a worse prognosis than their older counterparts.

Although in general, young women are treated similar to older patients, treatment modalities are different according to the stages of the disease, age at diagnosis and the presence of comorbid condition. In most cases, options for treatment are based on clinical tumour, lymph nodes and distant metastasis staging (Greene, 2002), including clinical factors such as lymphovascular invasion, histopathology grade, hormone receptor status (HER2) overexpression, comorbidities, and menopausal status are also very important. The treatment for breast cancer is multimodal, including surgery or locoregional treatment and systemic treatments. The factors influencing surgical treatment options are including tumour size, tumour position, cosmetic outcome, prior to radiation or any contraindication to radiotherapy, and patient's preference (Gabriel & Domchek, 2010). Options for locoregional treatments of breast carcinoma include breast-conserving surgery (BCS) with radiation therapy (RT) or a mastectomy (Eiermann & Vallis, 2012). Systemic treatment of breast cancer comprises administration of chemotherapy, hormonal therapy or targeted therapy. There are geographical differences in type of surgical treatment assignment among breast cancer patients. For instance, in Asian countries, mastectomy remain a common surgical treatment among Malaysia patients (n=591[51.2%]) (N Bhoo-Pathy et al., 2014). In Singapore, rates of mastectomy remained high over the past 10 years, which ranging from 43 to 59 % intake among breast cancer patients (P. M. Y. Chan et al., 2015) and similarly in Hong Kong (n= 2310 [51.5%]) patients were more likely to receive mastectomy as primary treatment at early stage of breast cancer (S. W. W. Chan, Cheung, Chan, & Cheung). In contrast, studies from Western countries reported high breast conserving therapy rates (n= 92,504 [70%]) in early stage breast cancer patients (S. Agarwal, Pappas, Neumayer, Kokeny, & Agarwal, 2014).

Radical mastectomy or Halsted mastectomy based on the principle established by Halsted and colleagues, was the standard surgical treatment for most patients regardless of the stage of their disease up to 1980s (Litière et al., 2012). Since surgery was an only option forty years ago, many patients were treated using Halsted's procedure. Consequently, these patients tend to lose not only the breast but also the entire underlying muscles, axillary lymph nodes and pectoral muscles. Also, it often results not only severe disfigurement but weakened arm function and disabling lymphedema (Feigenberg, Zer, & Dintsman, 1977). Based on Halsted's theory, the growth of breast cancer tumour cells appeared to be slow and disseminate from breast to lymph nodes and later to other segments of the body (Halsted, 1894). Following that, Halstead concluded that application of more aggressive surgery may reduce the likelihood of patients experiencing cancer recurrences, despite the fact that this surgery resulted in disfigurement of the body. Halstead procedure and his theory on breast cancer was widely accepted by physicians worldwide for decades (Umberto Veronesi et al., 2002).

After some time, Ian MacDonald, a cancer surgeon from Canada began challenging Halsted's procedure (MacDonald, 1951). While the nature of any cancer including breast can be determined biologically, he questioned whether radical mastectomy was important for all women with breast cancer especially those presented with slow-growing tumours. Also, this extensive surgical procedure did not result in a marked improvement in patient's survival. Eventually, MacDonald's theory was accepted by few surgeons and in early 1950s, patients had an option between radical mastectomy and simple mastectomy (MacDonald, 1951). However, there were some controversies as some surgeons considered performing simple mastectomy as equivalent to "malpractice" (MacDonald, 1951). At the same time, more patients were concerned of their surgical treatment and

started to question the effectiveness of the Halsted procedure. In early 1960s, Bernard Fisher, a well-known surgeon-scientist who showed a great interest in breast carcinoma investigation in both part of clinical side and laboratory, who became the first chair of the National Adjuvant Breast and Bowel Project (NSAPB). In 1971, the first randomized clinical trials was launched (NSAPB-04) in United States of America comparing radical mastectomy with simple mastectomy, or simple mastectomy accompanied by radiation therapy under the supervision of Fisher. This trial which included 1700 patients enrolled at 34 institutions, concluded that, there were no significant difference in survival outcomes for patients irrespective of surgical treatment. Based on the findings from NSAPB-04 and other clinical trials, the efficacy of simple mastectomy was confirmed and used as optimal treatment option for breast cancer patients. (De Laurentiis et al., 2008). Efforts by Fisher had successfully help to the omission of Halsted radical mastectomy option, which is severely disfiguring approach and had been the optimal breast cancer treatment for decades.

Nevertheless, later on the question arose whether the affected breast part could be preserved in patients presenting with less invasive tumor features such as small tumors, negative lymph node involvement and lower grade tumors without compromising survival (Litière et al., 2012). Besides, Fisher also revealed that, the breast cancer tumour cell incorporating with immunologic process or other mechanism may have chances trigger human body to demolish residual tumour by combining with systemic cytotoxic agents. These concepts has brought physicians to investigate more on breast conservative therapy for breast carcinoma, in combination with dissection of axillary, application of radiotherapy or systemic therapy of chemotherapy to the residual breast for better disease control (Fisher, 1977). The first randomized trials demonstrating breast conserving

therapy began in the 1970s, in conjunction with more widely utilization of mammographic screening mainly to detect small lesion and allow to determine breast cancer to be diagnosed at an early stage. The first trial was published by Veronesi's group in Milan using five-years results (Umberto Veronesi et al., 1981). This trial reported no difference between quadrantectomy following radiotherapy following axillary dissection and radical mastectomy. In 1985, Fisher et al. (Fisher et al., 1985) reported finding on five-year studies comparing lumpectomy with "total mastectomy" that omitted the whole breast, pectoral fascia, and axillary contents en bloc. However twenty-year follow-up by (Umberto Veronesi et al., 2002) and ("Consensus statement: treatment of early-stage breast cancer. National Institutes of Health Consensus Development Panel," 1992) studies finalized that breast conserving surgery is equivalent to mastectomy in term of survival outcome, as a treatment for breast cancer. Breast conserving therapy can be stated as "complete clearance of the breast tissue with a concentric margin of surrounding healthy tissue performed in a cosmetically acceptable manner (lumpectomy) followed by radiation therapy" by the International consensus conference (Schwartz et al., 2007). As a result, the affected breast could be preserved safely without removing the entire part of the breast. In general breast-conserving surgery is able to eradicate any disease that has been identified surrounding breast or regional lymph nodes, but unidentified cancer cells may remain in conserved breast either locally (i.e ,in the residual breast tissue, scar area, chest wall, or regional lymph nodes) or at distant sites. This disease or tumour cells if left untreated, can cause of locoregional recurrence or distant metastases, or both (Group, 2006). The effectiveness of radiation therapy and surgery on locoregional disease and on cause-specific death in early stage of breast cancer have been widely studied and many randomized trials were done over the past half-century. From the findings of Early Breast Cancer Trialists' Collaborative Group (EBCTCG), administration of radiation therapy right after breast preserving surgery has resulted in risk reduction of local recurrence, and

slightly reduce the mortality risk of breast cancer. These findings revealed that by eradicating left over tumour cell in the preserved breast using radiation therapy has decrease the chances for both cancer recurrence and distant metastasis disease (Group, 2011). Application of breast conserving surgery with radiation therapy lower the number of local recurrence and improves disease-specific survival rates to rates equivalent to those with mastectomy (Clarke et al., 2005). The proven effectiveness of radiotherapy treatment following breast conserving surgery which helps in eradicating the subclinical tumour margins of the disease has widened the practice of breast conserving therapy (Litière et al., 2012).

Breast conserving therapy was recommended as the standard treatment for most patients presenting with early stage breast carcinoma (stage I and Π) by the National Institutes of Health (NIH) in 1990. This recommendation was based on a some published randomized controlled trials reporting equivalent survival outcome between patients receiving BCT and those receiving mastectomy (M Blichert-Toft et al., 1991; Fisher et al., 2002; Fisher et al., 1989; Jatoi & Proschan, 2005; Lichter et al., 1992; Sarrazin et al., 1989; J. Van Dongen et al., 1991; Umberto Veronesi et al., 1981). In addition, 20 years follow-up by the National Surgical Adjuvant Breast and Bowel Project B-06 (Fisher et al., 2002) and the Milan trial (Umberto Veronesi et al., 2002) also confirmed that there was no difference in survival rates after a long follow up.

Although breast conserving surgery is associated with greater success among female in early-stage breast carcinoma, it may not a good option for female who are at high risk of breast cancer and local recurrence. Furthermore, patients presented with multifocal

disease (two or more gross lesions in different quadrants, diffuse microcalcifications on mammography) and local recurrence after breast conserving surgery, BCT may not be a suitable option (Recht, 1996) for BCT and where mastectomy is necessary. Also, in women with large tumour-to-breast ratio and small breast, breast conserving therapy is not the best option. However, some women presented at early-stage breast carcinoma may also undergo mastectomy instead of BCT due to contraindications to radiation therapy or some personal opinions.

Furthermore, there are a variety of psychosocial factors that may influence woman's option of cancer therapy especially in younger women. These include emotional distress, financial problems, and difficulties in access to appropriate medical care. A retrospective study including 577 breast cancer patients who were diagnosed at the age below 50 years old, reported that female younger than 35 years old are become emotionally unstable or stress and weak than older patients prior to the initial treatment (Gabriel & Domchek, 2010). Given that breast carcinoma is primarily known as a disease for postmenopausal women, with incidence pattern showing a modest premenopausal peak in the fifth decade of life (Rocco et al., 2013) a detection of breast malignancy in a young women may give a shock and lead to distress. However, married women or women who had a stable partner and family seems to be less likely to face emotional distress (Ganz et al., 2003).

Several other findings showed that young survivors experience a poorer quality of life following diagnosis compared to older survivors (Baucom, Porter, Kirby, Gremore, & Keefe, 2005) . In fact, this short-term reduction in quality of life stems from the effects of medical treatment received (Avis, Crawford, & Manuel, 2005). Treatment modalities

play an important role in young women's coping mechanism and their routine lifestyle. Young women often have fears and concerns of treatment impacts on their fertility and breast cancer development stage. The effects of surgery and breast removal resulted in more negative feelings regarding body image, affecting their intimate relationship and sexuality with their spouses (Marie Catherine Lee et al.). By receiving systemic treatment, many have experienced a sudden onset of menopause, which lead to the presence of hot flushes, as well as vaginal dryness leading to decreased sexual desire. Along with this, the demands of treatments not only effect the marital intimacy but also reduce the chance of breastfeeding in young mothers who lost their breast (Northouse, 1993). Apart from it, young working women may have to be away from work as they require frequent medical care such as radiation therapy after breast conserving surgery, where patients need to visit clinic 6-8 weeks to complete the therapy (Thewes, Butow, Girgis, & Pendlebury, 2004). Also, some have reported that the whole breast treatment including chemotherapy and radiotherapy caused fatigue or restriction from moving, increasing dependence on family members for certain needs (Thewes et al., 2004). All these will have a negative impact on patients and their families. Another reason which may affect treatment option in young women is the cost of mastectomy, and in the case of BCT, cost and distance to nearest radiotherapy center. Even though BCS associated with shorter hospital stays and less complications, but this therapy requires a compulsory radiation therapy later on. After all, total costs of BCS plus radiation therapy might equal or even exceed those of mastectomy (Barlow et al., 2001). A study by Goyal and colleagues have reported that, accessibility to radiotherapy such as travelling distance much time consuming which act as major barriers to receiving BCS in women with early stage breast cancer (Goyal, Chandwani, Haffty, & Demissie, 2015). Therefore, many patients prefer to receive mastectomy or breast conserving surgery alone over breast conserving surgery following radiotherapy just to avoid prolong course of daily treatment involved with

radiotherapy, that needs most frequent radiotherapy on daily basis to the whole breast followed by a boost to the tumor bed, delivered over the course of 6-7.5 weeks after the breast conserving surgery. Another study investigated the preferences of an urban versus rural patient to undergo mastectomy, which included accessibility of radiotherapy as a factor (Jacobs, Kelley, Rosson, Detrani, & Chang, 2008). By using the SEER database, Jacob and colleagues observed a significant changes in rates of mastectomies between women in the urban population (44% received mastectomies) and rural population (59% received mastectomies). The accessibility to radiation therapy shown to be much higher in urban population compared to rural population resulting in high rates of BCT in urban population. The accessibility of radiotherapy therefore is an important key for access to BCT. Access to medical care become a main concern in choice of surgical treatments. For instance, in case of insurance coverage several results have pointed the differences in medical care that occur between patients with health insurance and those without health insurance. Two studies documented that the higher proportion of BCT intake was associated with private health insurance. Breast conserving therapy relatively high in women possess health insurance compared with women without health insurance (Lautner et al., 2015; Voti et al., 2006). A study using data from Kentucky Cancer Registry documented that, status of health insurance was significantly associated with breast cancer treatment, for instance exclusion of adjuvant radiotherapy intake after breast-conserving surgery (Roetzheim et al., 2000). Also another study reported breast cancer survivors who did not possess health insurance often associated with poor survival outcome compared with those have private health insurance (Ayanian, Kohler, Abe, & Epstein, 1993). In addition, three studies have reported that BCT was more expensive than mastectomy due to the additional radiation treatments (Desch et al., 1999; MUNOZ, PACE, & WISE, 1991; Norum, Olsen, & Wist, 1997). Many women may therefore opt for mastectomy owing to the high cost associated with radiation therapy. Even with

reasonable cost of treatment and increased insurance coverage, it remains possible that women from lower socio-economic status might be unwilling or hard to take time off from work to undergo radiotherapy.

The option of surgical treatment is also influenced by the age factor such as age at diagnose. Age act an independent risk factor for receipt of non-standard breast-cancer therapies. Clinically, age was considered as a major factor in receiving radiotherapy among women at begining stage breast cancer. This is because older survivors often associated higher comorbidity, low tolerance for treatment, and shorter life expectancy, which may have a negative influence on survival outcome (Huang et al., 2017). Therefore, women are known to undergo different surgical treatments, depending on their age (Ballard-Barbash, Potosky, Harlan, Nayfield, & Kessler, 1996; Greenfield, Blanco, Elashoff, & Ganz, 1987; Silliman, Guadagnoli, Weitberg, & Mor, 1989). Followed by, the recent guidelines of the International Society of Geriatric Oncology and the European Society of Breast Cancer Specialists (EUSOMA) suggested the option of breast conserving surgery following radiotherapy or mastectomy followed by postoperative radiotherapy is selective depending on patient's age.

While many approaches have been emphasized on improving the quality of life in breast cancer patients, less invasive surgical method such as breast conserving surgery allows preservation of quality of life. Breast preserving surgery is considered the standard treatment of care for breast cancer at beginning stage. Importantly, breast preserving surgery help to maintain or restore appearance and preserve self-image, thus becoming a suitable option for young women with breast cancer.

1.2 Problem statement

While the BCT rates in beginning stage of breast cancer has increased rapidly in the US and Europe whereby over 60% of early stage breast cancer patients have received BCT, following the NIH consensus conference in 1990 (Lazovich, Solomon, Thomas, Moe, & White, 1999; M Catherine Lee et al., 2009; McGuire et al., 2009; Smith et al., 2009), however, a gradual reversal in the trend is being observed in the US over the last few years (Kummerow, Du, Penson, Shyr, & Hooks, 2015; Mahmood et al., 2013; McGuire et al., 2009). The reasons for the decline in rate of BCT in the US had been attributed to the increasing utilization of genetic testing for identify BRCA status, tumor characteristics such as triple negative breast tumors (Kummerow et al., 2015), receiving preoperative breast MRI (Mahmood et al., 2013), increased patient demand for surgeries with availability of immediate breast reconstruction,

In tandem, the rates of BCT in Asia remain low (Hiotis, Ye, Sposto, & Skinner, 2005), as shown in studies conducted in Malaysia (N Bhoo-Pathy et al., 2014) , Singapore (S.-E. Lim et al., 2007a), and Hong Kong (Yau et al., 2009). The reason for the low rates of BCT in Asia is not fully understood. Previous studies on Asian breast cancer survivors indicate that ethnicity is significantly associated with type of surgery, and several hypotheses have been developed to explain this association. Higher mastectomy rate have been reported in certain ethnic group (M. Tan, 2016) and being of Asian descent is known to be an independent predictor of mastectomy in a few studies (S. H. Lim et al., 2014; Lucas et al., 2015). The possible reasons cited for such include cultural preferences and smaller breast volume reported in Asian women (S. H. Lim et al., 2014; Yau et al., 2009). For instance, a hospital-based study in Malaysia reported that the Chinese breast cancer

patients were significantly prefer to receive mastectomy even after accounting for their age at diagnosis of breast cancer, status of menopausal, and tumour sizes (N Bhoo-Pathy et al., 2014). The possible reasons reported were, their breast sizes, which is smaller compared with the Malays and the Indians ethnicity and also the fear of undergoing extended treatment such as radiotherapy after surgery (Wong, Chen, Bottorff, & Hislop, 2008). Also the option for mastectomy among Chinese women might reflect their culturally driven perceptions such as, breast cancer disease will be completely eliminated (M. M. Lee, 2002; Wong et al., 2008) and overestimate the treatment will be the best option which may prevent recurrence with promising "100%" cure compared with breast conserving therapy option (Wong et al., 2008). Surgeon's choice and recommendation for BCS or mastectomy based on tumour size in relation to breast size and multicentricity maybe also be one of the reason (Teh et al., 2014). This is because centrally located tumours are relative contraindications to breast conserving surgery. Although reasons have been cited on controversies of surgical options and trends in young women, the actual reason is still unclear.

Although there are many epidemiological evidences on breast conserving therapy and mastectomy have been reported, most of them were conducted on western setting and a few studies have been carried out in the Asian region .While breast cancer occurrence in Asian setting is different from Western setting in terms of geographical difference, ethnic information, genetic difference, sedentary lifestyle, environmental factors, socioeconomic status, the presence of risk factors, accessibility of screening mammography, stage at diagnosis of disease, and the availability of appropriate health care (Hortobagyi et al., 2005), cultural belief, thus these difference may confound the application of western based knowledge into Asian women. To our knowledge, there is

no study done by comparing breast conserving therapy and mastectomy and also the time trends on type of surgical treatments choice in Asian women. To our knowledge, there is no study comparing BCT over mastectomy and also the time trends on type of surgical treatments choice among Asian women.

By using large hospital-based breast cancer registry dataset from Malaysia, Singapore and Hong Kong, we sought to evaluate survival outcomes with mastectomy and breast conserving therapy in young women with breast cancer in the Asian setting. Apart from studies conducted in Western settings, there is currently lack of knowledge on the trends in BCT and mastectomy in early stage breast cancer patients from Asian settings.

1.3 Justification of the study

To our knowledge there is no recent published observational studies comparing survival following breast conserving therapy and mastectomy in young breast cancer patients from Asian settings. Only few studies concerning this topic have been performed, often with small sample sizes. Therefore, this study will provide useful information on surgical treatment patterns and the associated survival outcomes among young Asian breast cancer patients. This information will be most useful for counseling young breast cancer patients during process of decision-making regarding suitable treatment and facilitating them in making surgical choices. Also the findings from this study may be beneficial for healthcare providers to tailor their treatment recommendations appropriately and for future cost-effective studies.

1.4 Research question

1. Is there a difference in overall survival between mastectomy and breast conserving therapy in young women with breast cancer in an Asian setting?
2. What are the time trends of breast conserving therapy in young Asian women with breast cancer?

CHAPTER 2: LITERATURE REVIEW

2.1 SEARCH STRATEGY

2.1.1 Search method

Literature review process done by searching the bibliographic database by using PubMed and Google Scholar. The search term in combinations obtain citation with relevant populations with related medical subheading term and text word. The terms used for search were ‘breast cancer’, ‘choice of surgery, ‘breast conserving therapy’, ‘mastectomy’, ‘survival or mortality’, ‘young women’, ‘treatment trend’. In addition reference lists of all notable reviews and findings were also searched. The ‘Endnote’ software was used to site the literature.

2.1.2 Selection of studies

The literature search was included all the published articles and papers starting from 1981 to recent years. Articles were excluded if it consist of case series or case reports and were not in English. The inclusion criteria were:

i. Published reports of randomized clinical trials and cohort studies.

ii. Studies related to the choice of surgical on young breast cancer patients in an Asian and Western settings.

iii. Outcome of the study mainly is about overall survival or disease-specific survival.

2.2 LITERATURE REVIEW

2.2.1 Breast cancer

Breast carcinoma is the most commonly diagnosed cancer among women that is currently increasing in incidence throughout the world. Based on the estimation of The World Health Organization (WHO) nearly 84 million people will die within 10 years between 2005 and 2015 due to cancer without any intervention (Rahman, 2011). Recent update on mortality rate in the United States stated that, one in four deaths was due to cancer (Jemal, Center, DeSantis, & Ward, 2010). Since breast cancer often associated with both high mortality and morbidity rates it has been highlighted as an important public health problem.

Table 2.1 Breast cancer staging (anatomic stage/prognostic groups)

Stage	Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastases (M)	Definition
Stage 0	Tis	N0	M0	Breast cancer cells remain inside the breast duct, without

				invasion into normal adjacent breast tissue
Stage IA	T1	N0	M0	Breast cancer is 2 centimeters or less and is confined to the breast (lymph nodes are clear)
Stage IB	T0 T1	N1mi N1mi	M0 M0	
Stage IIA	T0 T1 T2	N1 N1 N0	M0 M0 M0	The size of tumor is more than 2 centimeters but no larger than 5 centimeters Or it has spread to the lymph nodes under the arm
Stage IIB	T2 T3	N1 N0	MO M0	
Stage IIIA	T0 T1 T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 MO M0	Also known locally advanced cancer. The size of tumor is more than 5 centimeters across Or the cancer is extensive in the underarm lymph nodes
Stage IIIB	T4 T4 T4	N0 N1 N2	M0 M0 M0	
Stage IIIC	Any T	N3	M0	

				Or it has spread to other lymph nodes or tissues neat the breast
Stage IV	Any T	Any N	M1	The cancer cells has metastasized to other parts of the body.

Adapted from American Joint Committee Cancer, AJCC 7th Edition, 2009.

2.2.2 Global trends in breast cancer incidence

Breast carcinoma is the typical cancer and is noted that the most dominant cause of cancer deaths among female all over the country. Initially, breast cancer incidence rates were high in more developed region of the world, in urban populations (such as North America, Europe, Australia, New Zealand, Japan) representing 59% of new cases (Youlden et al., 2014). Therefore, it is not surprising that tremendous evidences on breast cancer epidemiology studies were mainly from research conducted from the Caucasian setting. This is maybe due to high rates of breast cancer cases and adequate resources supply, these regions have aided in intense laboratory and clinical research successfully. It has been reported that, almost 1.7 million new breast cancer cases were diagnosed in 2012 (25% of all cancers), which is relatively high proportion and expected to continue to increase in future (P. L. Porter, 2009). It is known that over the next two decades; in 2008, the trend has changed, where the increased incidence rates were noticed in both less and more developed countries with little higher cases from less developed site (883, 000 cases) than in more developed (794, 000) countries (Organization, 2014). However, the major problem often raised when discussing breast cancer incidence as global is limitation

of breast cancer data, only limited data available in many countries. Current data on breast cancer incidence are from small geographic areas which has been merged and expanded to large regions. Many reported cases perhaps comprise of the women who are more convenient to reach or who are from high socio-economic background. Thus, recent global figures unable to present the unrevealed socio-economic and cultural variation which influencing in increased incidence. It seems countries with the most organized cancer registries have showed increases in incidence of breast cancer. For instance breast cancer rates in Japan, Singapore, and Korea have doubled or tripled in the past 40 years, and China has reported 20 to 30% even though East Asian women known to have lowest rates of breast cancer compared to United States and Western Europe. This can be explained by the changing lifestyle patterns and the lack of proximity to effective clinical resources in both developed and developing regions. Worldwide trends on breast cancer reported that in developing countries, a rising burden of cancers associated with "Westernization" of the developing world (Ferlay et al., 2015). Firstly, desirable changes in socioeconomic status that increase life expectancy and allow women concern on reproductive control. Secondly, by practicing unhealthy dietary habits and lack of physical activity increases breast cancer risk. Thirdly, delayed childbearing, lower parity, less practicing breast-feeding and high use of hormone-replacement therapy. These behaviors have been practiced by Western countries hence the high prevalence of breast cancer compared to lower-income countries. Besides, reproductive factor such as early age at menarche, intake of western diet, low level of physical activity and high body mass profile all of these could lead to increase in risk of breast cancer. It shown that, the trend towards early menarche which mainly observed in Western setting are now seen in financially low-income countries. Therefore, by giving more important on early-life changes in physical activity and dietary habits may help to understand explanations on increasing incidence of breast cancer in the developing countries (P. Porter, 2008).

2.2.3 Global trend in breast cancer mortality

Breast cancer noted as the fifth cause of death from overall cancer-related death (522, 000 deaths) and it is the most typical death causing cancer among females especially in less developed regions (324, 000 deaths, 14.3% of total), followed by second cause of cancer death in more developed countries (198, 000 deaths, 15.4%) after lung cancer (Organization, 2014). Although breast carcinoma incidence has been escalating in most parts of the world, there are great inequity between high income and low income countries. It is reported that, in more developed countries rates of breast cancer incidence remains high, while in less developed countries mortality rates is relatively much higher. The reason for such patients presented at advanced stage of cancer and limited access treatment facilities. For instance, in Western Europe, breast cancer incidence has reported nearly more than 90 new cases per 100 000 women annually, compared with 30 per 100 000 in eastern Africa. In contrast, mortality rates of breast cancer in these two regions are almost same, at about 15 per 100 000, that clearly related to the late-stage disease presentation lead to much poorer survival in Eastern Africa (Ferlay et al., 2015). The overall higher mortality rate in "more developed" countries was accounted based on the high incidence of the breast cancer in these countries. In contrast, the mortality of breast cancer in "low developed" countries was due to high and imbalance distribution rate. Even though the ratio of mortality rate to incidence rate worldwide is (0.35) much lower, high MR:IR ratio in Africa (0.69) was noted compared to in North America (0.19) reflects majority of women from African countries diagnosed with late-stage cancer (P. L. Porter, 2009). This may be due to the variation in geographical distribution and socio-economic profile in these countries. A study conducted in Sub-Saharan Africa

documented up to 90% of the women diagnosed at late stage of cancer (stage III or VI), bigger tumors (median of 10 cm) and extensive intraductal component with lymph node metastases. Also, the treatment offered for breast cancer limited to surgery only because of the advanced stage and limited access to diagnostic imaging as well as adjuvant therapy. These advanced stage tumours cannot be treated successfully in the most optimal setting, therefore mastectomy became the only option for majority of the cases. Breast cancer awareness is relatively very low in most low-income countries, followed by low knowledge on breast cancer's treatment cause patients to undergo an aggressive treatment in a perception that aggressive treatment will result fast recovery (Fregene & Newman, 2005). This is further compounded by inadequate access to medical treatments. Due to the rapid change in global distribution of incidences, breast cancer will continue to give more burden on public well-being for most females especially in Asian, Africa and South America., Asia-Pacific region including East and South-East Asia as well as Oceania.

2.2.4 Breast cancer incidences and mortality in Asian women

Findings focused on Asian women revealed that, almost quarter (24%) of entire breast cancer cases was detected in Asia-Pacific region is (approximately 404, 000 cases with rate of 30 per 100,000), with highest incidences rate from China (46%), Japan (14%), and Indonesia (12%). The elevated incidence rate of breast cancer in Eastern Asia is observed in Japan and South Korea (both 52 per 100, 000) and for South-Eastern Asia the highest rate seen in Singapore (65 per 100, 000) (Youlden et al., 2014). Despite of increasing incidence rate observed in most Asian countries, overall incidence rates tend to be much lower for women in Asia (even the gap is decreasing) compared to West. Also the difference in age group at diagnosis, with highest being in the group of 45-50 age range

in most Asian countries, whereas a median of 55-60 years old is common in most Western countries (S. P. Leong et al., 2010; Toi et al., 2010). In Japan, the peak age at diagnose is 50years. Although it has remained the same over the last 25 years, the number of breast cancer cases has increased in every 10-year. While in Korea, the same age-specific pattern as Japan was seen, where the number of cases continued to increase with the time between 1996 and 2006. However, age-specific rates remains higher in Australia and New Zealand in comparison to Asian countries among young women below 50 years old (Youlden et al., 2014). It seems that, breast cancer risk factors were same all over the world, although most of etiological studies widely done in western settings. The differences in age at diagnosis between two settings can be explained in terms of use of population-based mammography breast cancer in western countries by target women aged 50 years and above. Hence, these programs often over-diagnosed asymptomatic breast tumors which is not progress further and also have tendency to alter the true incidence rates among women over 50 years old. Moreover, adaptation of " Westernized" culture by many Asian could be the reason of elevated breast cancer incidence in Asian-Pacific regions (P. Porter, 2008). Cultural changes have been identified mostly in young women, who staying in urban area of low and middle income countries (Green & Raina, 2008). For examples, adverse changes in diet, physical activities and fertility are associated with the changes. Women reproductive matters is one of the crucial factors of development of breast cancer disease among Asian young women. These are including late menopause, early menarche, giving first delivery at older age, and lower parity, which have significant potential in development of breast cancer disease. Also, acceptance of family planning concept among younger women, has allowed in declines in fertility rates across the region. Other factors which may influence the difference across countries include socio-economic level, adequate use of mammography and stability of cancer registry data. It is known that, higher number of breast cancer cases often associated with

financially higher income status, accessibility to breast cancer screening and areas where well-organized to collect full population-based cancer cases. Apart from that, clinical issues such as tumor types become one of the cause in disparity in age at diagnosis between both developed and less developed regions. For instance, most cases in Asian presented with estrogen or progesterone receptor negative (ER-/PR-), which may need more aggressive treatments (Green & Raina, 2008; S. P. Leong et al., 2010). It can be seen in a study conducted in Malaysia, the percentages of ER+ breast cancers escalated by 2% for every 5 years cohort between 1994 and 2008 (Youlden et al., 2014). The reason may be due to the rapid increase of ER+ cases while the incidence of ER- cases remained fairly stable, bringing on higher proportion of ER+ cancers over time. Breast cancer mortality is varied between countries, where rapid increase found in a few Asian countries contradicting with decrease in both Australia and New Zealand. Worldwide cancer survival study has been done recently, which was comparing 5 years survival of cancer of 67 countries including 16 Asian countries. About 80% or higher 5 years breast cancer survival was reported in 5 countries within Asia. These countries are China (80.9%), Israel (86.7%), Japan (84.7%), Korea (82.7%), and Qatar (85.3%). Survival rates was lower than 70% in Malaysia (67.8%), and India (60.4%), and very low in Mongolia (56.5%).The rapid increase in survival was observed in China, from 53.8% in 1995-1999 to 80.9% in 2005-2009. Small increased in survival was noticed in Malaysia from 64.8% in1995-1999 to 67.8% in 2005-2009, also similar flow in Japan but starting at much higher level (81.8% in 1995-1999, 84.2% in 2000-2004, and 84.7% in 2005-2009). Besides that, another study by Youlden and colleagues have noticed a huge difference in mortality rates of breast cancer following age group across Asia-Pacific region. There were significant differences in mortality trends by age in several countries in which trend data are available. The rapid increasing in mortality rates regardless of the age at death were noticed in China and Thailand. In contrast, larger decrease in mortality rates was

noticed in Australia and New Zealand for women aged 50 years and below compared to those 50 years or older. In Hong Kong, a significant decrease in mortality rate was reported in women aged below 50 years old while mortality rates were stable for women aged 50 years and over. Besides, in Japan and Singapore, mortality rate of breast cancer decrease gradually in younger women but increasing in older women; and in Malaysia, Philippines and South Korea, although breast cancer rates were increasing in both young and old women, the rate of increase was lower for women aged below 50 years old. In summary, death rate of breast cancer was either decreasing more rapidly, or increasing gradually in slower pace, for women aged below 50 years old compared to those who were above 50 years old. It was observed in developed country like Japan and Singapore which showed the significant decrease in mortality for younger women compared to a significant increase in the mortality rate of breast cancer among those who are older. These disparities in breast cancer survival mainly influenced by the efficacy of early detection and access to appropriate treatment in countries. Others factors including, cultural and economic barriers in breast cancer management, such as misconception on treatment management for the disease (undergoing surgery will cause cancer cell to spread rapidly), lack of awareness, inappropriate diagnostic tools and treatment facilities. All these factors may potentially alter the treatment decision and adherence of breast cancer disease giving on high mortality rate in Asia-Pacific region. The major problem highlighted was delayed presentation, many women in less developed Asian countries usually presented with advance stage of disease. This advance stages usually associated with large tumor with poorly differentiate, more lymph nodes involved or distant metastases which are hardly treatable. Since access for mammography in many developing countries is too limited, most of the women with breast cancer in Asia-Pacific region are only diagnosed after severe symptoms appear. Thus, resulting in high number of women with advanced stage breast cancer. However, mammography screening have

been shown to be greatly used in Western countries may won't be that effective for women in Asians. It is uncertain in Asians women often reported with smaller volume breasts with higher breast density. This might limit the sensitivity of mammography screening and by application of more sensitive tools (ultrasound) for dense breast might result in over sensitive among Asian women. Hence, a study conducted in Japan reported that mammogram screening program is better than clinical examination on identifying breast carcinoma at early stage in Japanese women. This followed by finding from Singapore observed the spectrum of mammographic deformity which resulted almost same with what would estimated in a Caucasian population. In addition socioeconomic development strongly associated with the treatment standards among Asian countries. For instance, in low resources countries breast cancer diagnosis and treatment facilities highly insufficient leading to a poor prognosis and survival rates. These countries often faced challenges such as, lack of education and awareness regarding breast cancer, inappropriate pathology facilities and unorganized care system with respect to adjuvant and systemic treatments. Despite, in middle resources countries (China, Indian, Malaysia, Trukey and Iran) the challenges are more on poor quality of data registries, inappropriate multidisciplinary organization, and insufficient resources prioritization of breast cancer control programs, consistency in socioeconomic growth lead to promising upgrades in breast cancer treatment and survival rates in these countries. It was noticed that, in both low and middle resources countries in Asia, the allocation of government spending on health is remain low. While in the high resources countries such as Japan, Korea, Singapore, and Taiwan the survival of breast cancer reported relatively favorable, due to well-establish cancer control and cancer care systems with adequate financial support at the national level by their government. Owing to lower concern on health expenditure in most Asian countries especially on female breast cancer, these patients often do not receive sufficient knowledge on treatment option even they presented at early medical

intervention. Apart from it, there was marked differences in tumor profile and ethnicity in breast cancer survival among Asian women. Triple negative breast cancer, known as cancer tumor with lack of estrogen and progesterone receptors and no over expression of human epidermal growth factor lead to a worse prognosis compared to other molecular subtype. It has been reported, the proportion this type of breast cancer found to be high among Asian region compared to North America and Europe. In addition, ethnicity was reported to act as an independent factor of breast cancer survival in Asian-Pacific region. In multiethnic countries like Malaysia and Singapore, poorer survival was documented in Malay women compared to Chinese and Indian women. The reason was breast cancer tumor entity in Malay ethnicity tend to be more aggressive with higher risk of axillary lymph nodes metastasis, compared to Chinese and Indian women with similar size of tumors. Among Asia, despite low incidences of breast cancer was noticed in most developing countries, rapid increase in countries with huge population such as China and Japan which will prolong to divert the worldwide burden of breast cancer in Asia. Since Malaysia is a multiethnic country, data was investigated according to the ethnic groups of Malay, Indian and Chinese. It was observed that the pattern was similar in the three groups, with decreasing incidence in post-menopausal women (D Max Parkin, Bray, Ferlay, & Pisani, 2005).

2.2.5 Breast cancer in Asian versus Western settings

Breast cancer incidence seemed to be vary between regions and countries, highly influenced by differences in racial and ethnic group, health care resources, and lifestyle practice (Hortobagyi et al., 2005; D Maxwell Parkin & Fernández, 2006; P. Porter, 2008). Knowing that, female in more developed countries tend to have less children, pregnancies

at older age and less practice breastfeeding, all of these factors will add to the risk of breast cancer (P. Porter, 2008). The lifestyles factor such as, high intake of alcohol, use of oral contraceptives and hormone replacement therapy, along with lack of physical activity, increases the risk of breast cancer (Organization, 2014). Also, genetics factors has account for small part of the worldwide variation in the incidence of breast cancer (D Maxwell Parkin & Fernández, 2006). On the other hand, some screening programs in developed regions of world, which noted to be accountable for the over-diagnosis of some cancers which might otherwise have continue to exist undetected (Paci, Warwick, Falini, & Duffy, 2004; Svendsen, Olsen, & Lynge, 2006). It was reported by some articles assessed on breast cancer incidence rates in West world including the United Kingdom, Canada, Australia, Sweden and Norway, that rapid increase was noticed after introduction of population screening program, incidence rate remained significantly higher than estimated in subsequent years (Jørgensen & Gøtzsche, 2009). In contrast, among less developed countries with lower incidences of breast cancer may be related to number of cases remained undiagnosed due to inappropriate diagnostic and healthcare facilities (G. Agarwal et al., 2009; Anderson et al., 2011). This may lead to incomplete data stemming from unorganized cancer registry system from these countries. Hence this problem was also faced by developed regions (Igene, 2008). However, due to steep increase in incidences in the countries with low rates of breast cancer, it has contributed to the drastic changing in perspective of breast cancer control.

2.2.6 Breast cancer in young women

Breast carcinoma (BC) diagnosed among younger women poses substantial clinical problem in term of bio-molecular, genetic and psychological studies, and oncologic

treatment. Breast cancer in young women is unexpectedly impactful, owing to the fact that these women might have young children, diagnosed at very young age, future plan to conceive, and may be in the middle stage of their career life (Baum et al., 2003). Breast cancer clinical procedures and treatment option of young BC patients differ substantially with their older counterparts. This was also revealed by the Surveillance, Epidemiology, and End Results (SEER) database in the United States where 75% of breast cancers was reported in women aged > 50 years, whereas only 6.5% of women aged < 40 years, and 0.6% of women aged < 30 years were diagnosed with breast cancer (Zhou & Recht, 2004). Generally breast cancer occurring in young women has higher rates of pathologic features associated with more aggressive cancer such as, extensive intraductal component, higher grade of tumor histology, bigger size of tumor, necrosis, over-expression of HER2, absence of the estrogen receptor, higher S-phase fractions, and more abnormal expression of p53 (Agrup, Stäl, Olsen, & Wingren, 2000; Albain et al., 1993; Marcus, Watson, Page, & Lynch, 1993; Nixon et al., 1994), detected at late stage and often resulted worse outcome comparing breast cancer occurring in older patients. In the study done by Anders and colleagues, that targeted on gene expression in between females survivors younger than 45 and over 65 years of age, 367 genes were identified, that might differentiate tumours of young women with lesions found in women older than 65. This findings confirmed that breast cancer detected in young patients aged below 45 years old is biologically different when compared to tumor detected in females aged 65 years old and over (H.-B. Lee & Han, 2014). Early diagnosis in this young age group may be somehow difficult. In many cases, mammography screening is not adequate and unable to identify cancer lesions in young women due to high breast density. All the above factors may lead to a worse prognosis in young breast cancer patients. Several findings have supported this hypothesis; two population-based studies showed that risk of breast cancer was highest in youngest and the oldest study cohorts by compared with the intermediate age (Adami,

Malker, Holmberg, Persson, & Stone, 1986; Kollias, Elston, Ellis, Robertson, & Blamey, 1997). Based on a finding using the National Cancer Data Base, a very young women with age < 35 years were shown to have more advanced cancer at the time of diagnosis and a poorer 5-year survival compared to their older counterpart (Winchester et al., 1996). Similar studies have been reported using databases from SEER (Swanson & Lin, 1993), the Finish Cancer Registry (Holli & Isola, 1997), the Southwest Oncology Group (Albain et al., 1992), and Danish study in which young patients did not receive adjuvant therapy. A study from the Institute Curie demonstrated that, despite patients treated with mastectomy or BCT, breast carcinoma diagnosed among very younger women was related with poorer 5-year survival rate than older women (Zhou & Recht, 2004).

2.2.7 Breast cancer management

While breast carcinoma is the most typically diagnosed cancer with almost one quarter of women diagnosed with breast cancer in the worldwide, it is often associated with good prognosis compared to other type of cancers. Therefore, the primary goal of breast cancer treatment is to monitor and regulate the disease with the goal of achieving cure and good quality of life. The objective of treatment modalities is to obtain good survival outcome, reduce the chances of distant metastases or local recurrence, good cosmetic and figure, relief of symptom and to pertain satisfactory quality of life same as possible to the life before detected with breast cancer. By obtaining sufficient knowledge on breast cancer therapies, it may useful for physicians and patients in decision-making and care for their patients during and after cancer treatment. Breast cancer treatments consist of surgery, radiotherapy, systematic therapy (chemotherapy and hormonal therapy) and targeted treatment on HER2. Generally, the treatment assignment for breast cancer patients are

based on their stage, tumour category, and biomarkers of diagnosis. For instance, for breast cancer stage I and II, mastectomy or breast conserving surgery plus radiation therapy often become the best treatment option. Application of radiotherapy after breast conserving surgery resulted decreases in death rate and local recurrence of breast cancer (Coombes et al., 2004). In the case of stage III breast cancer, it's required intake of chemotherapy to scale down the tumor size to ease for breast conserving surgery. Usually the option on adjuvant systematic therapy treatment (chemotherapy) will depends on factors such as involvement of lymph node, hormone receptor status, HER2 status, patient age and their menopausal status.

2.2.7.1 Breast cancer surgery

Surgery is the oldest and most predominant method, which has been applied widely as the primary treatment of breast cancer. It remains as an important treatment modality which aimed for a total disease control by discarding the primary tumour . The history of surgical treatment first started from the American Surgeon named William Stewart Halsted who had a number of amputated breasts and a satisfactory post-operative follow ups. Halsted's radical mastectomy (RM), demonstrated in 1894, involved resection of entire breast, pectoralis muscles, and regional lymphatics (Halsted, 1894). While radical mastectomy resulted in a relatively low rate of local recurrence, it was unable to achieve better curative level. Trial on radical mastectomy, which involved dissection of internal mammary was unsuccessful to provide improved survival outcomes. Several attempts have been made to improve surgery techniques and resulted in difference of treatment techniques such as modified radical mastectomy, total mastectomy, and more lately skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM) (Rahman, 2011).

Consequent to that, the era of the breast surgery started and Halsted surgical intervention was introduced and remained as choice of surgical, until the 1950's when the breast conservative treatment associated with adjuvant radiotherapy appeared. Despite of some evidence that support modified radical mastectomy as less aggressive techniques compared to radical mastectomy, patients are however subjected to a loss of breast part. Subsequently, the use of breast conserving therapy techniques stemmed from the attempt to preserve involved breast part, where it involves resection on the part of breast containing the cancer without compromising survival. This evolution on surgery therefore, have contributed to knowledge in the context of improving the care, anesthesia, early screening and the improvement in the use of radiotherapy and the measurement of their dosage, besides informing the patients and their participations in the treatment decision process.

2.2.7.2 Breast conserving therapy

Breast conserving surgery (BCS) or lumpectomy is crucial step of breast conserving therapy (BCT), which involved removing of the primary tumor with or without surgical staging axilla, following administration of radiotherapy to eliminate the margin or microscopic residual of the disease. This procedure acted as an optimal primary therapy for the majority of women with Stage I or II breast cancer. It is known as highly preferred treatment because it able to provide survival outcome equivalent to the total mastectomy by preserving the breast (Fisher et al., 2002). On the other hand, it often diminishes the psychological distress due to mastectomy treatment. In such case of absence of reasons for opting mastectomy, the option on both BCS and mastectomy can be made by considering patient's background and personal preferences.

Table 2.2 Patient's selection for BCT

✓ Physical examination history
✓ Clinical Breast Imaging
✓ Pathology reported of the resected breast
✓ Patient's requirements and exceptions

2.2.7.3 Surgical technique

Breast conserving therapy is not only focused on preserving the affected breast part, but also in providing anesthetically satisfied result. The cosmetic outcome after BCT is highly influenced by the surgical factors such as: size and positioning of dissection, management of the lumpectomy cavity and extent of axillary dissection. Therefore the surgical techniques may lead to some differences. The aim of the surgery is to provide cosmetically successful outcome without incorporating local tumor control. Therefore, several procedures need to be taken by surgeon when designing the incision such as the position of the lump, type of incision, deepness of mass from the skin and the incision had to be near to the lump to avoid further tunneling process. Breast conserving surgery usually followed by additional radiation therapy for 5-6 weeks after the surgery.

2.2.7.4 Radiotherapy

Generally, radiation therapy will be administrate to patients right after breast-conserving surgery to treat subclinical margins. A randomized controlled trials (RCTs) comparing breast-conserving surgery with and without radiation demonstrated that taking radiation therapy after surgery resulted significant reduced in five-year local recurrence rate, in spite of the use of adjuvant systemic therapy (7 versus 26 percent; number needed to treat ([NNT]=5), and appeared to reduce the 15-year breast cancer mortality risk (30.5 versus 35.9 percent; NNT = 18) (Clarke et al., 2005). However, radiation therapy is quite costly and time consuming, which may be one for the reason patients opt for mastectomy.

2.2.7.5 Mastectomy

Mastectomy is surgery involving the complete removable of the breast tissue without preserving breast. It is widely used surgery for women diagnosed with breast cancer as well as a prophylaxis to reduce the risk of breast cancer in high-risk women. Basically, mastectomy is performed to patient with contradiction for breast conserving therapy, patients who personal requested for mastectomy, and for some prophylactic purposes to reduce the risk of breast cancer.

i. Surgical techniques

The effective mastectomy was achieved by understanding the complex structure of the chest wall and axilla in order to ensure resection procedure of breast tissue with preservation of maximum muscular function and sensation.

ii. Selection for mastectomy

A mastectomy treatment usually performed in the case of breast conserving therapy is contraindicated or unsuccessful such as;

Table 2.3 Factors influencing mastectomy

✓ Patients presenting with multicentric breast cancer with two or more primary tumours in separate quadrants of the breast
✓ Diffuse suspicious or malignant-appearing microcalcifications on mammography
✓ Patients with history of previous therapeutic radiation that included a portion of the affected breast
✓ Pregnancy during breast cancer is an absolute contraindication on receiving radiation therapy
✓ Failure to obtain negative resection margins after reasonable attempts at re-excision ✓ Widespread disease that is unable to corporate by local excision of a single region or part of breast tissue that achieves negative margins with a good cosmetic result.
✓ Patients presenting with larger tumor size >5cm (category 2B) in relation to breast size
✓ Patient's preference to undergo a mastectomy compared breast conserving therapy for some reasons, including a personal wish or need to avoid postoperative radiation, screening, cosmetics concerns or biopsies.

- ✓ Prophylaxis, for patients with hereditary breast and ovarian syndrome and patients with mutations of the breast type 1 and 2 susceptibility genes (BRCA 1 and BRCA 2) may have high risk of ipsilateral breast recurrence or contralateral breast cancer by undergoing breast-conserving therapy, a prophylactic bilateral mastectomy reduces the risk of developing breast cancer by more than 90%

(Hartmann et al., 2001; Rebbeck et al., 2004)

However, lately the proportion of mastectomy appear to have increased for other reasons, including race, younger age at diagnosis, utilization of pre-operative magnetic resonance imaging , patient's socioeconomic status, accessibility to a radiation facility, surgeon quantity and specialty training, and availability of experts in advances in reconstructive surgery (Onitilo, Engel, Stankowski, & Doi, 2015).

2.2.7.6 Adjuvant therapy

Following locoregional therapy (surgery +/- radiotherapy), female with early-stage of breast cancer also receive adjuvant systemic therapies as additional treatment. These include chemotherapy, endocrine therapy, and targeted therapies substantially reducing cancer recurrence and breast cancer specific death. Breast cancer with regional nodal involvement benefits most from systemic therapy (Wood, 2015). Chemotherapy is the optimal treatment of care for female with lymph node-positive cancer or tumors larger than 1cm. Breast cancer with hormone receptor-negative cancer derives more benefit from chemotherapy than hormone receptor-positive cancer (Goldhirsch et al., 2007). Factors including age and comorbidities highly influence the decision to use

chemotherapy. Most of the studies suggested a modest benefit obtained from treatment with antracyclines or taxanes than other chemotherapies ("Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005, 365: 1687-1717. 10.1016/S0140-6736(05)66544-0,") particularly in women with tumours overexpressing ERBB2 (Pritchard et al., 2006). A finding from systematic review of 12 studies reported overall and disease-free survival advantages most when a taxane-containing regimen applied for premenopausal and postmenopausal women presented with early stage breast cancer (Ferguson, Wilcken, Vagg, Ghersi, & Nowak, 2007). Also, meta-analysis including 13 RCTs demonstrated that adding a taxane to an antracycline-based regimen improved disease-free survival (five-year risk reduction = 5 %) and overall survival (five-year risk reduction = 3%) (De Laurentiis et al., 2008). Endocrine therapy, such as tamoxifen, Selective Estrogen Receptor Modulators (SERMs), aromatase inhibitors, and gonadotropin-releasing hormone agonists, are only effective in breast cancer patients with tumours expressing hormone receptors. It has been shown five years of treatment with tamoxifen decreases disease-specific death of breast cancer (absolute risk reduction = 9.2% over 15 years; NNT=11) compared to no treatment ("Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005, 365: 1687-1717. 10.1016/S0140-6736(05)66544-0,").

2.2.7.7 Breast conserving therapy versus mastectomy

Studies reported that female with localized breast cancer are equally to survive regardless they underwent breast conserving therapy or a mastectomy. Nevertheless similar survival outcomes of cancer obtained, but there are several factors need to be considered when deciding between breast conserving therapy and mastectomy.

Table 2.4 Factors associated with surgical treatment

Factors	Surgical treatment
Tumour size	Larger tumour and small breasts size advised to undergo mastectomy rather than BCT
Extensive DCIS	Extensive ductal carcinoma in situ known as a very early cancer normally not response to chemotherapy and mastectomy was recommended in order to remove all the disease.
Tumour margins	In the case of large amount of tissue has been removed and the margins are still involved after BCS, mastectomy may be required.
Radiation	Long term side effect of receiving radiotherapy
Risk reduction	Patients tend to receive mastectomy to reduce the risk of future breast cancers. Particularly for a woman who carries a breast cancer gene mutation.
Individual preference	Preserve or remove breasts.
Risk of second breast cancer	Among very young women and women with a known breast cancer gene mutation, these women may consider bilateral mastectomy is not only treat the known

	cancer, but also to prevent chance of second cancer in the future. Women with a strong family history of breast cancer, such as family members in every known generation (mother, grandmother, great grandmother), are still candidates for BCT, but may wish to undergo bilateral mastectomies

Table 2.5 Previous findings on breast conserving surgery versus mastectomy

Study Period, Authors and Publication time	Outcomes of study
Three-year OS (nine studies) [(R Arriagada et al., 2003; Fentiman et al., 2003; Fisher et al., 2002; Jacobson et al., 1995; H.-D. Lee et al., 1997; U Veronesi et al., 1995)]: 92.8% (1975 of 2129 patients in group BCT) compared with 94.4% (1419 of 1503 patients in group MT); OR (fixed effect model) 0.84, 95% CI (0.63-1.12), *P* = 0.64.	There was no statistically significant difference between group BCT and group MT

Five-year OS (twelve studies) [(R Arriagada et al., 2003; M Blichert-Toft et al., 1991; Fentiman et al., 2003; Fisher et al., 2002; Jacobson et al., 1995; Montague, Ames, Schell, & Romsdahl, 1984; J. Van Dongen et al., 1991; U Veronesi et al., 1995)]: 82.6% (2726 of 3300 patients in group BCT) compared with 83.5% (2492 of 2985 patients in group MT); OR (random effects model) 0.97, 95% CI (0.84-1.11), *P* = 0.64.	There was no statistically significant difference between group BCT and group MT
Ten-year OS (eight studies) [(R Arriagada et al., 2003; Fisher et al., 2002; Jacobson et al., 1995; Montague et al., 1984; J. A. van Dongen et al., 2000; U. Veronesi et al., 1977; Umberto Veronesi et al., 2002)]: 69.7% (2085 of 2992 patients in group BCT) compared with 69.3% (2014 of 2906 patients in group MT); OR (random effects model) 1.09, 95% CI (0.97-1.23), *P* = 0.16.	There was no statistically significant difference between group BCT and group MT
Fifteen-year OS (six studies) [(R Arriagada et al., 2003; Fentiman, 2000; Fisher et al., 2002; Poggi et al., 2003; J. A. van Dongen et al., 2000; Umberto	There was no statistically significant difference between group BCT and group MT

Veronesi et al., 2002)]: 56.2% (1447 of 2576 patients in group BCT) compared with 58.6% (1107 of 1888 patients in group MT); OR (random effects model) 0.90, 95% CI (0.80-1.02), *P* = 0.10.	
Twenty-year OS (five studies) [(R Arriagada et al., 2003; Fentiman, 2000; Fisher et al., 2002; Poggi et al., 2003; Umberto Veronesi et al., 2002)]: 44.1% (938 of 2128 patients in group BCT) compared with 45.0% (661 of 1468 patients in group MT); OR (random effects model) 1.09, 95% CI (0.95-1.25), *P* = 0.23.	There was no statistically significant difference between group BCT and group MT
Three-year locoregional recurrence rate (five studies) [(R Arriagada et al., 2003; H.-D. Lee et al., 1997; U Veronesi et al., 1995)]: 3.2% (59 of 1860 patients in group BCT) compared with 1.9% (12 of 631 patients in group MT); OR (random effects model) 1.52, 95% CI (0.40-5.69), *P* = 0.54.	There was no statistically significant difference between group BCT and group MT
Five-year survival locoregional rate (ten studies) [(R Arriagada et al., 2003; M Blichert-Toft et al., 1991; Fisher et al., 2002; Lichter et al., 1992; J. A. van	There was no statistically significant difference between group BCT and group MT

Dongen et al., 2000; U Veronesi et al., 1995; Zhang & Kong, 2006)]: 7.4% (305 of 4111 patients in group BCT) compared with 7.1% (151 of 2137 patients in group MT); OR (random effects model) 1.19, 95% CI (0.77-1.85), *P* = 0.44.	
Ten-year locoregional recurrence rate (eight studies) [(R Arriagada et al., 2003; Fentiman, 2000; Fentiman et al., 2003; Fisher et al., 2002; Jacobson et al., 1995; Montague et al., 1984; J. A. van Dongen et al., 2000; Umberto Veronesi et al., 2002)]: 10.4% (385 of 3691 patients in group BCT) compared with 8.0% (218 of 2736 patients in group MT); OR (random effects model) 1.55, 95% CI (1.05-2.30), *P* = 0.03.	There was no statistically significant difference between group BCT and group MT
Fifteen-year locoregional recurrence rate (two studies) [(R Arriagada et al., 2003; Umberto Veronesi et al., 2002): 7.1% (78 of 1094 patients in group BCT) compared with 3.6% (16 of 440 patients in group MT); OR (random effects model) 1.59, 95% CI (0.84-2.98), *P* = 0.37.	There was no statistically significant difference between group BCT and group MT

Twenty-year locoregional recurrence rate (four studies) [(R Arriagada et al., 2003; Fisher et al., 2002; Poggi et al., 2003; Umberto Veronesi et al., 2002)]: 11.6% (288 of 2477 patients in group BCT) compared with 10.1% (115 of 1144 patients in group MT); OR (random effects model) 1.89, 95% CI (0.48-7.50), *P* = 0.37.	There was no statistically significant difference between group BCT and group MT

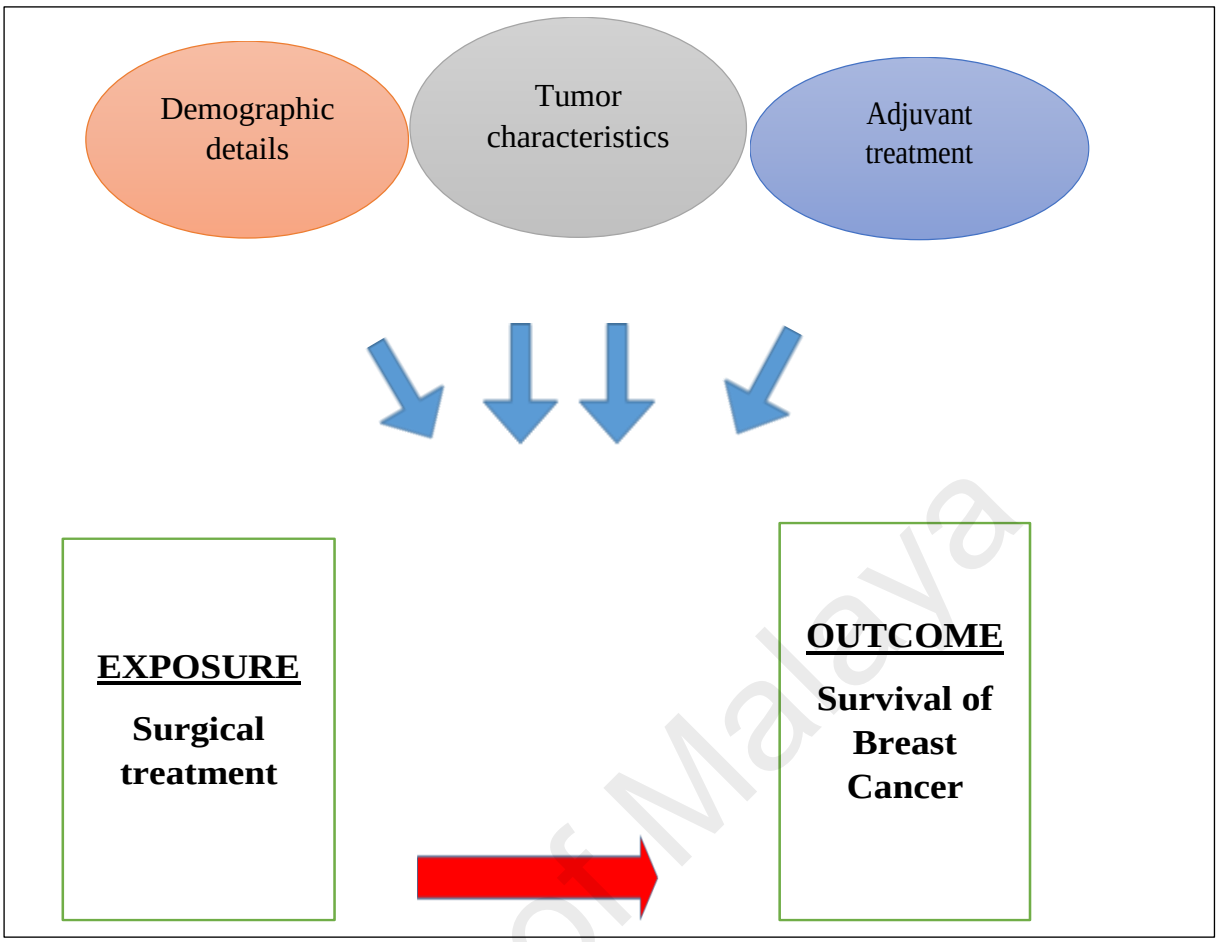

Figure 2.1: Flow chart of conceptual framework

2.3 CONCEPTUAL FRAMEWORK

This study included three main components which are confounders, exposure and outcome of the study. The confounding factors consist of breast cancer patient's demographic details, clinical characteristics and treatment details. This confounders were analyzed with the exposure (type of surgery) to obtain outcome (survival of the breast cancer patients).

2.4 OBJECTIVES

2.4.1 Primary objectives

1. To assess the impact of breast conserving surgery compared to mastectomy on overall survival in young Asian women (<50 years) with breast cancer.

2.4.2 Secondary objectives

1. To determine the pattern of breast conserving therapy use in young women with breast cancer in an Asian setting.

2.5 HYPOTHESES

2.5.1 Null Hypothesis

There is no difference in survival outcomes with either BCT or mastectomy in local treatment of early-stage breast cancer in young breast cancer patients.

2.5.2 Alternate Hypothesis

There may be difference in survival outcomes with either BCT or mastectomy in local treatment of early-stage breast cancer in young breast cancer patients.

CHAPTER 3: METHODOLOGY

3.1 Introduction

Data of this study were retrieved from the hospital-based breast cancer registries of four Asian oncology centers; the University Malaya Medical Centre (UMMC), Malaysia Breast Cancer Registry, National University Hospital (NUH), Singapore Breast Cancer Registry, Tan Tock Seng Hospital (TTSH), Singapore Breast Cancer Registry and Queen Mary and Tung Wah Hospital (QMTWH), Hong Kong. Demographic factors, clinical, pathological, treatment and outcomes data on breast cancer patients managed at the four participating centers were collected and analyzed. The goal of this collaboration study to examine the nature of breast cancer presentation, tumour details, management, and rates of survival in Asian women with breast carcinoma. Since observational research on breast carcinoma are lack in this part of the world, the Singapore, Malaysia and Hong Kong breast cancer working group was performed, which is an international, multidisciplinary collaboration involving epidemiologists, breast surgeons and oncologists of the University Malaya Medical Centre (UMMC), Malaysia, National University Hospital, (NUH), Singapore, Tan Tock Seng Hospital (TTSH), Singapore and Queen Mary and Tung Wah Hospital (QMTWH), Hong Kong. Following this approach, the breast cancer registries of these hospitals were jointed, to allow producing as much clinical studies on breast cancer and facilitate implementation of new research projects, including clinical trials and detailed molecular studies. The mission of the collaboration is to optimize the management, survival, functional status, and long-term quality of life of Asian breast cancer patients.

3.1.1 Data from Malaysia

University Malaya Medical Centre Breast Cancer Registry was started in 1993, comprising 6039 patients newly diagnosed with breast cancer between 1993 and 2012. Data on basic demography, clinical and pathological characteristics, and treatment details were collected prospectively for each patient using a written form (proforma) based on input from patient interview and medical records, as well as radiology and pathology reports. The details from proforma was gradually transferred into an electronic database and the database was audited for quality purpose. The UMMC Breast Cancer Registry is a prospective hospital-based registry of consecutive women newly-diagnosed with breast cancer since 1993. The registry has been approved by the institution's ethical review committee.

3.1.2 Data from Singapore

National University Hospital (NUH) is a tertiary comprehensive cancer centre in Singapore. A prospective Breast Cancer Registry was established in 1995 collecting data on demographics, tumour, treatment, and follow-up (S.-E. Lim et al., 2007a). The registry has been approved by the NUH Institutional Ethics Review Board. Tan Tock Seng Hospital (TTSH) is a tertiary government hospital in Singapore. A prospective hospital based cancer registry was started in 2001. The registry received approval from National Healthcare Group (NHG) Domain Specific Review Board (DSRB).For both registries each patient was entered into

the Registry Database, with baseline demographic and clinical information obtained from multiple sources, including patient interview, written hospital medical records, and electronic radiology/pathology reports.

3.1.3 Data from Hong Kong

Data for Hong Kong was prospectively collected from breast cancer patients treated in the Breast Surgery Division, Department of Surgery, Queen Mary (QMH) and Tung Wah (TWH) Hospital, the University of Hong Kong. Queen Mary Hospital is one of the largest acute regional hospitals of Hong Kong, and a teaching hospital of the medical school of the University of Hong Kong whereas TWH is the second largest general hospital in Hong Kong West Cluster. Public hospitals are placed into seven hospital clusters according to their locations in Hong Kong and managed by the Hospital Authority (HA) of the government of Hong Kong. QMH is the leading hospital of the Hong Kong West cluster and with TWH, its sister hospital, treat approximately 200 breast cancer patients a year not only from its catchment area but also receive referrals from other regional hospitals being a tertiary referral centre of Hong Kong (E. B. C. T. C. Group, 2005). Database covered all 8,961 women who were diagnosed with breast cancer between January 1, 1997 and December 31, 2001.A total of 7,630 (85.1%) medical records of women who were diagnosed with breast cancer for the period were successfully retrieved and reviewed both from the existing database of the University of Hong Kong and HKCaR. These records were matched with the HKCaR, Hong Kong Death Register, and databases from Hong Kong Hospital

Authority's data warehouse (Pritchard et al., 2006). This registry received approval from the Institutional Review Board of the University of Hong Kong.

3.1.4 Inclusion criteria

The inclusion criteria of the study:

a) Female patients with newly diagnosed, invasive breast cancer.

- From year 1990 to 2012

b) Young breast cancer patient's age below 50 years old.

3.1.5 Exclusion criteria

The exclusion criteria for this study included:

a) Patients without and unknown surgery type

b) Ductal carcinoma *in-situ* cases (stage 0)

c) Patients with stage III and IV breast cancer who are not suitable for BCT

d) Patients receive chemotherapy before surgery (neoadjuvant chemotherapy)

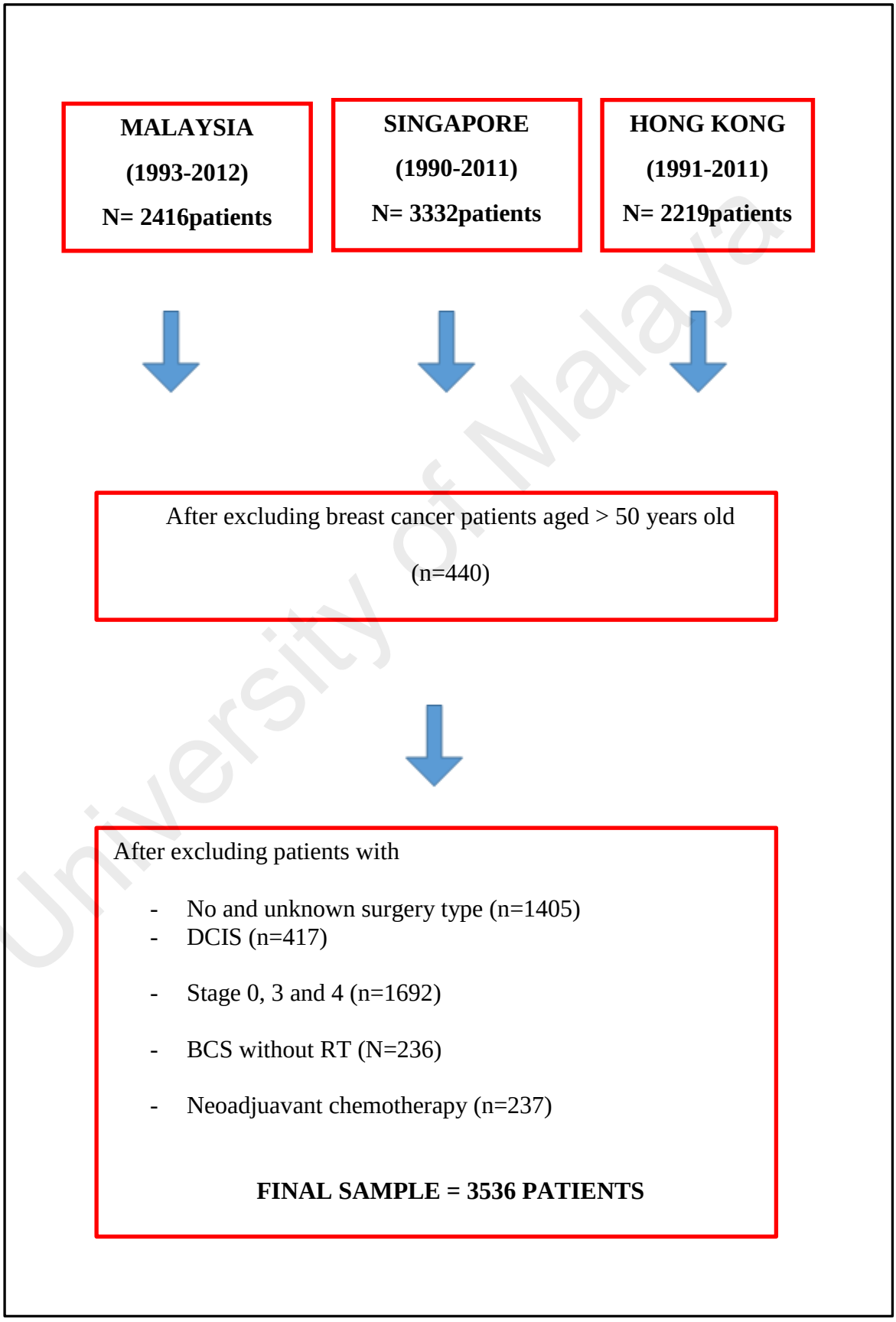

Figure 3.1: Flow chart of study selection

3.2 Study variables

This study consists of the following variables:

3.2.1 Patient characteristics

- Age at diagnosis
- Ethnicity
- Country

3.2.2 Tumour characteristics

- Tumor size at diagnosis (cm)
- Axillary lymph node status (no of nodes)
- Estrogen receptor (ER) status (positive, negative)
- Progesterone receptor (PR) status (positive, negative)
- Human Epidermal Growth Factor Receptor 2 (HER2) status (positive, negative)
- Tumor grade/ differentiation (high, moderate, low)
- Lymphovascular invasion (LVI) (present, absent)

3.2.3 Treatment details

- Surgery (mastectomy, breast conserving surgery)
- Hormone therapy (no, yes)
- Chemotherapy (no, yes)
- Radiotherapy (no, yes)

3.2.4 Follow up time

- Date of diagnosis
- Date of death
- Date of last follow-up
- Vital status

3.3 Patient's characteristics

In these three registries, data on basic demography of patients such as age at diagnosis, ethnicity and nationality were obtained. The major ethnic groups in Malaysia, Singapore and Hong Kong are Chinese, Malays, Indians and other minority ethnic groups. As such, we grouped patients' ethnicity using similar categories. Other details on reproductive history including information on breastfeeding, use of oral contraceptive, menopausal

status, use of hormone replacement therapy (HRT), and history of breast cancer were not available for a vast majority of patients. Data on comorbidities was also lacking. Currently, there is no standard definition for young women with breast cancer. In general, studies on young women with breast cancer have included women aged less than or equal to 50, 45, 40 or 35 years (Ankit Bharat, Rebecca L. Aft, Feng Gao, & Julie A. Margenthaler, 2009; Tarone, 2006; Villarreal-Garza et al., 2013). Also, many studies have described the 'very young' as less than 35, or 20-29 years (Althuis et al., 2003; Cancello et al., 2013; de Deus Moura, Carvalho, & Bacchi, 2015). The most common cut off points used by many studies was 50 years. This cut off points often reflects the menopausal status given that the average age at onset of menopause is 50 years (Boulet, Oddens, Lehert, Vemer, & Visser, 2008). In the circumstance of studies lacking in data on menopausal status, using this approach may be pragmatic. Therefore, threshold was set at 50 years old with patients aged below 50 years being classified as young women and hence included in the present study. In this study, we only include patients with history of breast cancer surgery as primary treatment and for those underwent breast conserving surgery must accompanied by radiation therapy.

3.4 Adjuvant treatment details

Loco-regional treatment was classified as surgery (mastectomy, breast conserving surgery [BCS] with radiotherapy). Administration of hormone therapy was categorized as yes and no and adjuvant chemotherapy (no chemotherapy, yes chemotherapy) will be included. Data for neoadjuvant chemotherapy was not included in this study because the aim of the study assessing breast cancer patients with surgery as primary treatment. In this study, we excluded patients without information on radiotherapy treatment after

breast conserving surgery and with information on radiation therapy after mastectomy surgery.

3.5 Follow up and outcome assessment

The important outcome of this study is all-cause mortality. Data on all-cause mortality was updated yearly through direct linkage with the respective National Registration Departments of Malaysia, Singapore and Hong Kong, which have the birth and death records of all nationals and cover the overall populations, as it is compulsory to register births and deaths in these countries. Follow-up time was calculated from the date of breast cancer diagnosis, to the death date or censored at end of follow-up (23rd March 2015 in UMMC, 31st July 2013 in NUH, 24th July 2014 in TTSH and 22nd August 2014). For patients with missing information such as vital status, date of death and date of last contact, attempts were made to trace their case notes or proforma. All four databases (UMMC, NUH, TTSH and QMTWH) were matched into a standard template and subsequently merged. Quality checks were carried out by cross-checked the results between the individual registries and the merged database to ensure consistency.

3.6 Study design

The study design that was used is historical cohort study using secondary data from four institutions in Malaysia, Singapore, and Hong Kong; University Malaya Medical Centre (UMMC, Malaysia), National University Hospital (NUH, Singapore), Tan Tock Seng Hospital (TTSH, Singapore), Queen Mary and Tung Wah Hospital (QMTWH, Hong Kong). All four hospitals are tertiary referral centres, with prospective

breast cancer registries since 1991 in QMTWH (Kwong, Mang, Wong, Chau, & Law, 2011), 1993 in UMMC, 1990 in NUH (S.-E. Lim et al., 2007b), and 2001 in TTSH (E. Y. Tan, Wong, Ang, & Chan, 2005).

3.7 Statistical analysis

Categorical variables were described by proportions and compared using the Chi square test. Continuous variables were expressed in medians and compared with the Mann-Whitney U test. Overall surgical treatment time-trends were analysed, followed by stratification by age at diagnosis, ethnicity and country.

Univariable logistic regression analyses were performed to assess the association between the demographic and clinical variables with breast conserving therapy status as the dependent variable. Overall survival was estimated using Kaplan-Meier analyses and compared by log-rank test. Propensity score (PS) was initially used to balance demographics, tumor and treatment characteristics, which were unequally distributed between the "breast conserving therapy" and "mastectomy" groups. Subsequently a Cox regression model adjusted by the PS of patients was fitted to estimate the effect of surgery type on overall survival.

Propensity score method is a commonly used statistical method in observational studies that adjusts the estimated treatment effect for confounding (Ferguson et al., 2007). Current study is an intervention study but observational in nature. Hence, it was expected to have potential selection biases in treatment assignment. A propensity score which is presented as a single summary score represents the relationship between confounding factors for non-treatment and treatment group assignment. This single score considers simultaneously all the relevant predictors of treatment and attempts to reduce selection

bias by weighting the confounding relative to their influence on predicting treatment group assignment (Rudner & Peyton, 2006). PS method serves as a better control for confounding factors compared with the conventional multivariable outcome modeling. This method also provide an estimation which is closer to the true marginal treatment effect than the estimate by log regression analyses (Martens, Pestman, de Boer, Belitser, & Klungel, 2008).

However, as PS is estimated using measured data, the method is unable to control for unmeasured or imperfectly measured variables (Stürmer, Schneeweiss, Avorn, & Glynn, 2005). Therefore, residual systematic bias cannot be excluded in certain cases. In this study, propensity score for breast conserving therapy was calculated for each patient. The PS for surgery type is defined as a patient's probability of being subjected to breast conserving therapy given her demographics, tumor and treatment characteristics, irrespective of whether the patient actually received BCT. Since the probability of receiving breast conserving therapy or mastectomy based on clinical practice which depends on the physician's and patient's decision, potential predictors that were highly influence this decision and associated with overall survival were identified (Brookhart et al., 2006). These variables included country, age at diagnosis, ethnicity, tumor size, tumour grade, number of lymph nodes involved, ER status, PR status, HER2 status, lympho-vascular invasion, status of chemotherapy, and status of hormone therapy. These variables were used in a multivariable logistic regression model as predictors with 'breast conserving therapy' as the outcome. From this model, the expected probabilities of receiving breast conserving therapy for each patient given their clinical variables (i.e. PS) were determined. Patients were subsequently grouped into twenty based on their propensity score.

Cox regression model was used to estimate crude all-causes of mortality risk with

hazard ratios (HRs) for overall survival comparing young breast cancer patients presenting with early stage breast cancer who were subjected to breast conserving therapy versus mastectomy. Entry time was date of diagnosis with breast cancer, and exit time was the date of death or date of last contact, whichever came first. Subsequently, the model was stratified by propensity score in twenty to ensure that within each stratum, comparisons were made for patients whom had similar expected probability of receiving breast conserving therapy and mostly, similar distribution of confounders. Subsequently the model was adjusted for PS as a continuous variable. The resulting HR therefore is an adjusted estimate of the effect of breast conserving therapy of breast cancer patients.

Subgroup analyses were performed as previous studies have shown that higher tumor grade, younger age, bigger tumor size, ER negative and HER2 negative tumor has higher risk of breast cancer-specific mortality and should be considered for adjuvant systemic therapy. As a form of sensitivity analysis, the main Cox regression model was stratified into quintiles of PS instead of adjusted for PS as a covariate.

Multiple imputation method was used to account for missing values (ranging between 5% and 30%). Missing values namely primary tumor size (10%), tumor grade (14%), no of positive lymph node involved (2.4%), ER status (8.3%), PR status (13.6%), HER2 receptor status (29.6%), LVI (20.4%), chemotherapy status (2.4%), and hormone therapy status (4.6%) were imputed by means of multiple imputation using the multiple imputation package in IBM SPSS Statistics Version 21. All variables of the multivariable adjusted model were included in the imputation model and 10 imputation sets were created.

Two-sided p values and hazard ratios (HR) for mortality, along with their 95% confidence intervals (CI), will be included in this analysis. For all analyses, our threshold

for statistical significance is 0.05. Data analysis will be performed using IBM SPSS statistics software version 21 software.

3.8 Ethical consideration

- UMMC Breast Cancer Registry has been approved by the Ethical Review Committee of University Malaya Medical Centre
- NUH Breast Cancer Registry has been approved by the Institutional Ethics Review Board
- TTSH Breast Cancer Registry received approval from National Healthcare Group (NHG) Domain Specific Review Board (DSRB)
- QMTWH Breast Cancer Registry received approval from the Institutional Review Board of the University of Hong Kong.

CHAPTER 4: RESULT

4.1 Introduction

This retrospective cohort study included 3536 women of 20-49 years old, representing 44.4% of the 7967 cases of pathologically proven early stage breast cancer patients presenting to four tertiary hospitals in Malaysia, Singapore and Hong Kong between 1992 and 2012. A total of 3536 patients (stage I and stage II) received breast surgery. Majority of patients were subjected to mastectomy 2245 (63.5%) while only 1291 (36.5%) patients received breast-conserving therapy in these settings.

4.2 Characteristics of independent

This study analyzed thirteen independent variables which were country, age and year of diagnosis, ethnicity, tumor size, tumor grade, status of lymph nodes involved, ER status, PR status, HER2 status, lymphovascular invasion, chemotherapy and hormone therapy status. The total number of breast cancer patients from each country was, (n=1278 [36.1%]) from Malaysia, (n=1035 [29.3%]) from Singapore and (n=1223 [34.6%)]) from Hong Kong. The median age of diagnosis of the overall cohort was 44 years old Majority of the breast cancer patients in the study were from Chinese ethnicity of (n=2479 [70.1%]) followed by Malay (n=381 [10.8%]), Indian (n=168 [4.8%]) and others were 508 (14.4%).

The median tumor size at presentation was 2.0 cm. Tumour grade was documented in 3015 patients and half of the breast cancer patients presented with moderately differentiated tumor (n=1359 [45.1%]) whereas 1152 [38.2%] patients presented with poorly differentiated tumor. About one third of the patients presented with lymph nodes positive breast cancer (n=952 [27.6%]). Almost 2/3 of our patients had positive ER receptors and positive PR receptors (65.4%, 62.0%) respectively. From 2488 patients, HER2 was over expressed in 604 patients (24.3%). Almost forty percent of breast cancer patients had tumors with lymphovascular invasion (n=1104 [39.2%]). Among patients subjected to surgery, a vast majority underwent mastectomy (n=2245 [63.5%]) patients, whereas 36.5% had breast conserving therapy to (n=1291). From 3452 patients, 2299 (66.6%) had received chemotherapy after surgery. Hormonal treatment was given to 1823 (88.6%) breast cancer patients with ER positive tumors.

4.3 Table 4.1 (Characteristics and treatment pattern of young breast cancer patients by type of surgery)

The patients who received BCT differed from those who received mastectomy by demographic and tumour characteristics. The median age of diagnosis in the overall cohort was 44 years old. The median age in patients receiving mastectomy was 44 years, whereas in those receiving breast-conserving therapy, median age at diagnosis was 43 years. The proportion of patients receiving BCT was highest in Malaysia (37.6%), followed by Singapore (33.3%), and lowest in Hong Kong (29.0%). Type of surgery was highly influenced by ethnicity whereby, Malay patients were the most likely to receive BCT whereas the Chinese patients were least likely to receive it.

Breast conserving therapy was significantly associated with small tumour size (median = 1.8 cm), compared to mastectomy (median tumour size = 2.3 cm). It was also significantly associated with less invasive tumour characteristics such as negative lymph nodes involvement, low-grade tumour, hormonal receptor positivity, and absence of lympho-vascular invasion. Out of 1884 (75.7%) patients with HER2 negative tumour, 1131 (73.1) received mastectomy and 753 (80.1%) received BCT. Patient subjected to BCT were also significantly less likely to receive chemotherapy (n=496 [38.7%]) compared with patients receiving mastectomy (n=1514 [69.7%]).

4.4 Figure 4.2-4.10 (Trend of age, country and ethnicity on type of surgery)

Overall, the proportion of patients receiving BCT modestly increased from 33% in 1996 to 40% in 2011 (Figure 2). Nevertheless, the overall mastectomy rates (60%) remained higher compared to breast conserving therapy (40%) in this cohort of young Asian women with early breast cancer. The surgical options by age at diagnosis showed that the rates of both breast conserving therapy and mastectomy in very young women (20-39 years old) remain unchanged from 1996 to 2011 (Figure 3), while a 13% increase in BCT rates was observed from 1996 to 2011 in young women aged between 40 and 49 years (Figure 4). Substantial differences in trends were observed between countries. While rates of BCT increased by approximately 20% over 15 years in Singapore, only a modest increase was observed in Malaysia, whereas no change in BCT rates were observed in Hong Kong (Figure 7).

In addition, we observed ethnic variations in surgical treatment pattern. Initially (1996-2000) there was a high number of Chinese patient (72%) receiving mastectomy,

however the rates of BCT gradually increased, and reached 42% in 2011 (Figure 8). Approximately 50% of Malay patients received BCT, and this number remained fairly constant from 1996 to 2011 (Figure 9). The proportion of Indian patients receiving BCT increased with time, reaching 50% in 2011.

4.5 Table 4.2 (Association of demographic, clinical and treatment characteristics with breast conserving therapy)

In univariable logistic regression analyses constructed to determine the factors associated with breast conserving therapy, country, age at diagnosis, years of diagnosis, ethnicity, tumour size, tumour grade, lymph nodes status, estrogen receptor, progesterone receptor, HER2, chemotherapy and hormone therapy were significantly associated with breast conserving therapy. Following multivariable adjustment, patients from Hong Kong were least likely to receive BCT (adjusted OR 0.62, 95%: CI 0.51 to 0.77) compared to Malaysian patients. Singaporean patients were more likely to be receiving BCT (adjusted OR 1.29, 95% CI 1.07 to 1.56) compared to Malaysian patients. There was also variation by ethnicity for BCT; Malay patients were observed to have a statistically significant two-fold likelihood of receiving BCT (adjusted OR 1.86, 95% CI 1.45-2.38) compared with Chinese patients. Patients presenting with bigger tumour size and older age at diagnosis of breast cancer were also more likely to receive mastectomy compared to BCT. Over expression of HER2 and LVI were inversely associated with BCT.

4.6 Figure 4.1 and Table 4.3 (Survival of breast cancer patients following breast conserving therapy and mastectomy).

Between 1992 and 2012, a total of 336 deaths were observed within 3536 patients. There was no difference in terms of survival between patients receiving BCT and mastectomy. Five-year OS was 94.9% (95% CI 93.5 to 96.3) for patients receiving BCT, and 92.9% (95% CI 91.7 to 94.1) for patients receiving mastectomy (Figure 1). The OS for ten years was 87.0% (95% CI 84.5 to 89.6) for patients receiving BCT and 84.8 (95% CI 84.6 to 85.0) for patients receiving mastectomy. Breast conserving therapy was not associated with a lower risk of mortality compared to mastectomy in both crude and adjusted Cox regression analyses. Following stratification by propensity score, the results remain unchanged (adjusted HR of 0.80 95% CI 0.63-1.02 for BCT compared to mastectomy).

Subgroup analysis within patients with TNBC, T1, N0, M0 tumours, and younger age at diagnosis (20-39 years) also revealed that the type of surgery was not significantly associated with survival outcomes in young breast cancer patients.

Table 4.1. Clinico-pathologic characteristics and treatment pattern of 3536 stage I and stage II young breast cancer patients by type of surgery.

Characteristic	Overall n= 3536	Type of surgery		P value[1]
		Mastectomy n= 2245	Breast conserving therapy n= 1291	
Country, n (%)				<0.001
Malaysia	1278 (36.1)	792 (35.3)	486 (37.6)	
Singapore	1035 (29.3)	605 (26.9)	430 (33.3)	
Hong Kong	1223 (34.6)	848 (37.8)	375 (29.0)	
Age in years, median	44	44	43	<0.001
Ethnicity, n (%)				<0.001
Chinese	2479 (70.1)	1578 (70.3)	901 (69.8)	
Malay	381 (10.8)	199 (8.9)	182 (14.1)	
Indian	168 (4.8)	111 (4.9)	57 (4.4)	
Others/Unknown	508 (14.4)	357 (15.9)	151 (11.7)	
Tumour size, cm median [2]	2.0	2.3	1.8	<0.001
Tumour grade, n (%)				0.010
Well differentiated	504 (16.7)	281 (15.0)	223 (19.4)	
Moderately differentiated	1359 (45.1)	859 (46.0)	500 (43.6)	
Poorly differentiated	1152 (38.2)	728 (39.0)	424 (37.0)	
Unknown	521	377	144	
Status of LN involved, n (%)				<0.001

Not involved	2499 (72.4)	1518 (69.5)	981 (77.5)	
Involved	952 (27.6)	667 (30.5)	285 (22.5)	
Unknown	85	60	25	
ER status, n (%)				<0.001
Negative	1121 (34.6)	743 (36.7)	378 (31.0)	
Positive	2123 (65.4)	1280 (63.3)	843 (69.0)	
Unknown	292	222	70	
PR status, n (%)				0.040
Negative	1161 (38.0)	753 (39.4)	408 (35.6)	
Positive	1896 (62.0)	1159 (60.6)	737 (64.4)	
Unknown	479	333	146	
HER2 status, n (%)				<0.001
Negative	1884 (75.7)	1131 (73.1)	753 (80.1)	
Positive	604 (24.3)	417 (26.9)	187 (19.9)	
Unknown	1048	697	351	
Lymphovascular invasion, n (%)				<0.001
Absent	1710 (60.8)	1037 (57.3)	673 (67.1)	
Present	1104 (39.2)	774 (42.7)	330 (32.9)	
Unknown	722	434	288	
Chemotherapy, n (%)				<0.001
No	1153 (33.4)	657 (30.3)	496 (38.7)	
Yes	2299 (66.6)	1514 (69.7)	785 (61.3)	
Unknown	84	74	10	
Hormone Therapy [3], n (%)				0.450

No	235 (11.4)	146 (11.9)	89 (10.8)	
Yes	1823 (88.6)	1086 (88.1)	737 (89.2)	
Unknown	65	48	17	

HER2: Human epidermal growth factor receptor, ER:estrogen receptor, PR:progestron receptor, LVI: Lympho vasucular invasion.

[1]Categorical variables were tested using Chi square test and continuous variables were tested using Mann Whitney. *P* value < 0.05 is considered statistically significant.

[2] Tumour size unknown in 352 patients

[3]Includes only patients with ER (+) tumours

Table 4.2. Factors associated with breast conserving therapy in stage I and stage II premenopausal breast cancer patients.

Characteristic	Overall (n= 3536)	Univariable	Multivariable[1]
Country, n (%)			
Malaysia	1278	1.00	1.00
Singapore	1035	1.16 (0.98-1.37)	1.29 (1.07-1.56)
Hong Kong	1223	0.72 (0.61-0.85)	0.62 (0.51-0.77)
Age in years	3536	0.98 (0.97-0.99)	0.96 (0.95-0.98)
Year of diagnosis	3536	1.04 (1.03-1.06)	1.02 (1.01-1.04)
Ethnicity, n (%)			
Chinese	2479	1.00	1.00
Malay	381	1.60 (1.29-1.99)	1.86 (1.45-2.38)
Indian	168	0.90 (0.65-1.25)	1.01 (0.70-1.45)
Others	508	0.74 (0.60-0.91)	0.90 (0.71-1.15)
Tumour size, cm	3536	0.68 (0.64-0.72)	0.67 (0.63-0.72)
Tumour grade, n (%)			
Well differentiated	609	1.00	1.00
Moderately differentiated	1593	0.75 (0.61-0.91)	0.91 (0.72-1.15)
Poorly differentiated	1334	0.75 (0.60-0.93)	1.14 (0.87-1.50)
Lymph node status, n (%)			
Not involved	2565	1.00	1.00
Involved	971	0.66 (0.56-0.77)	0.86 (0.71-1.04)
ER status, n (%)			
Negative	1271	1.00	1.00

Positive	2265	1.34 (1.11-1.62)	1.29 (0.98-1.70)
PR status, n (%)			
Negative	1397	1.00	1.00
Positive	2139	1.22 (1.01-1.47)	0.95 (0.75-1.20)
HER2 status, n (%)			
Negative	2481	1.00	1.00
Positive	1055	0.68 (0.55-0.84)	0.70 (0.57-0.85)
LVI status, n (%)			
Absent	2152	1.00	1.00
Present	1384	0.64 (0.54-0.76)	0.67 (0.55-0.81)
Chemotherapy, n (%)			
No	1188	1.00	1.00
Yes	2349	0.69 (0.60-0.80)	0.90 (0.74-1.08)
Hormone Therapy [3], n (%)			
No	1324	1.00	1.00
Yes	2213	1.17 (1.01-1.35)	0.90 (0.70-1.14)

[1]Derived from multivariable Cox regression analysis adjusted for (country, age at diagnosis, year of diagnosis, ethnicity, tumour size, tumor grade, lymph node status, ER status, PR status. HER2 status, chemotherapy status, hormone therapy status).

Table 4.3. Impact of type of surgery on overall survival in 3536 young women presenting with stage I and stage II breast cancer.

	Number of patients	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall cohort			
Mastectomy	2245	1.00	1.00
Breast conserving therapy	1291	0.80 (0.64-1.00)	0.82 (0.64-1.04)[1]
T0-1,N0 tumors	1234		
Mastectomy	628	1.00	1.00
Breast conserving therapy	606	1.10 (0.71-1.68)	0.95 (0.65-1.59)[2]
TNBC	496		
Mastectomy	304	1.00	1.00
Breast conserving therapy	193	0.61 (0.30-1.24)	0.58 (0.28-1.22)[2]
Age at diagnosis, 20-39	911		
Mastectomy	556	1.00	1.00
Breast conserving therapy	355	0.80 (0.55-1.17)	0.79 (0.53-1.19)[2]
Age at diagnosis, 40-49	2625		
Mastectomy	1689	1.00	1.00
Breast conserving therapy	936	0.79 (0.60-1.03)	0.84 (0.63-1.13)[2]

HR = Hazard ratio; TNBC = Triple negative breast cancer

[1] Derived from multivariable Cox regression analysis adjusted for propensity score in 20 (PS calculated using country, age at diagnosis, year of diagnosis, ethnicity, tumour size, tumour grade, lymph node status, ER status, PR status, HER2 status, Lympho-vasucular invasion, chemotherapy status, hormone therapy status)

[2] Derived from multivariable Cox regression analysis adjusted for propensity score in quintiles (PS calculated using country, age at diagnosis, year of diagnosis, ethnicity, tumour size, tumour grade, lymph node status, ER status, PR status, HER2 status, Lympho-vasucular invasion, chemotherapy status, hormone therapy status)

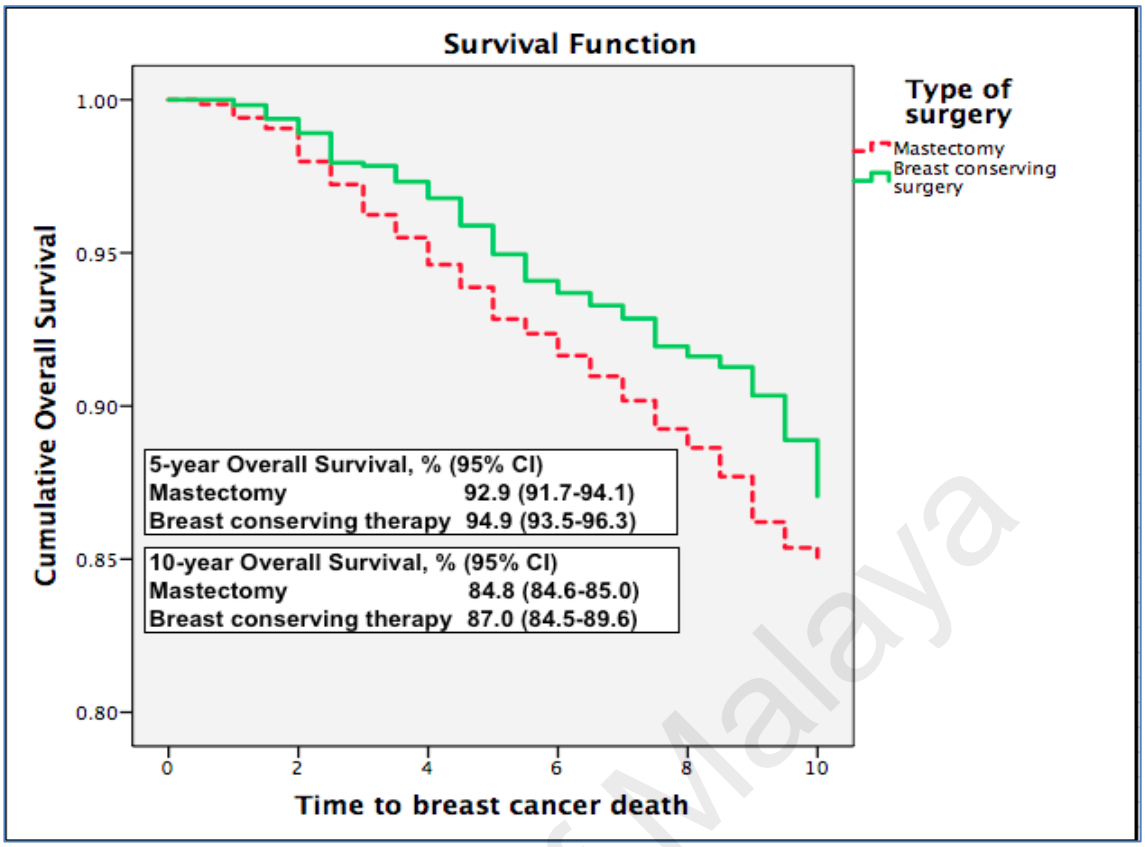

Figure 4.1: Overall survival estimates in 3536 young women presented with early stage breast cancer

Overall trend of surgical treatments for early stage breast cancer patients

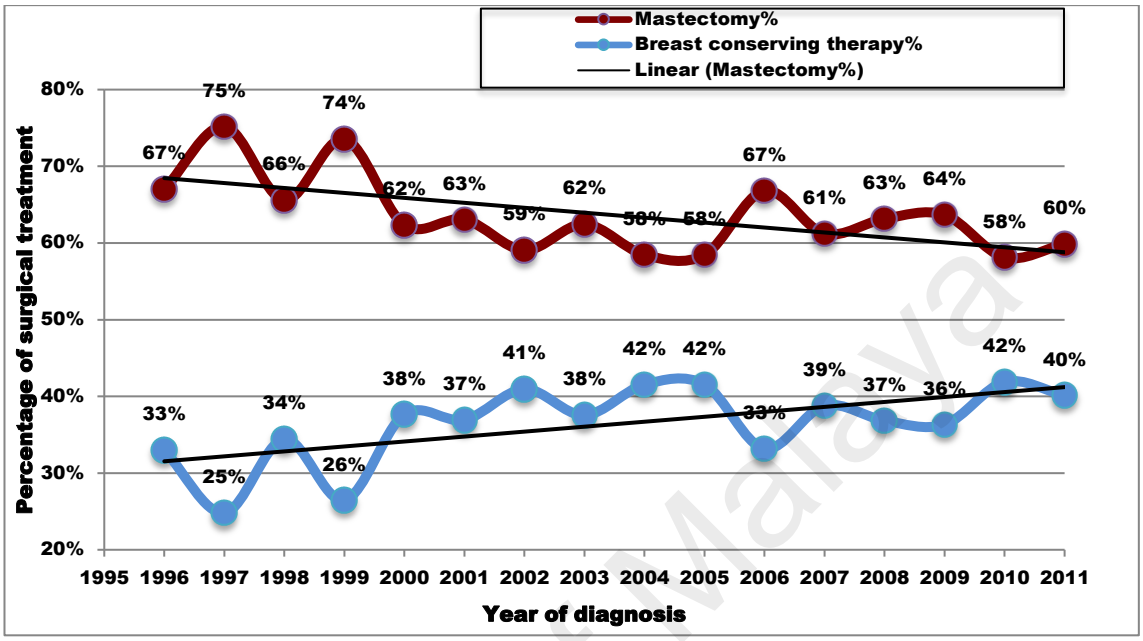

Figure 4.2: Proportion of women with early stage of breast cancer who underwent mastectomy (red line) and breast conservation therapy (blue line) by years of diagnosis.

AGE AT DIAGNOSIS

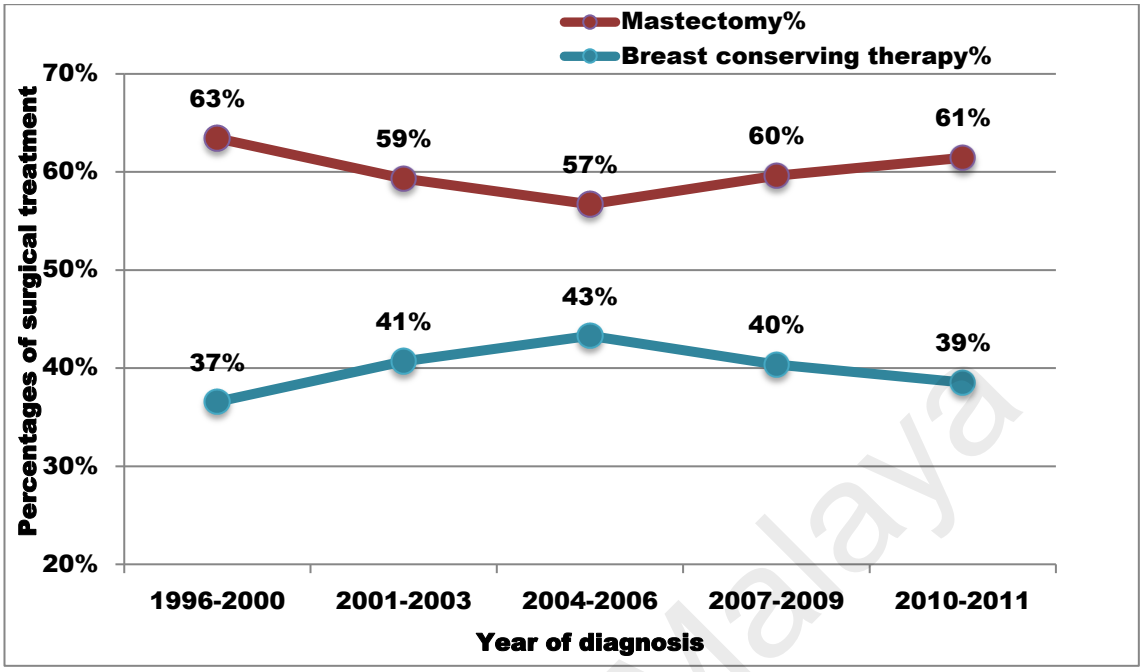

Figure 4.3: Proportion of women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line) by age at diagnosis20-39 years old.

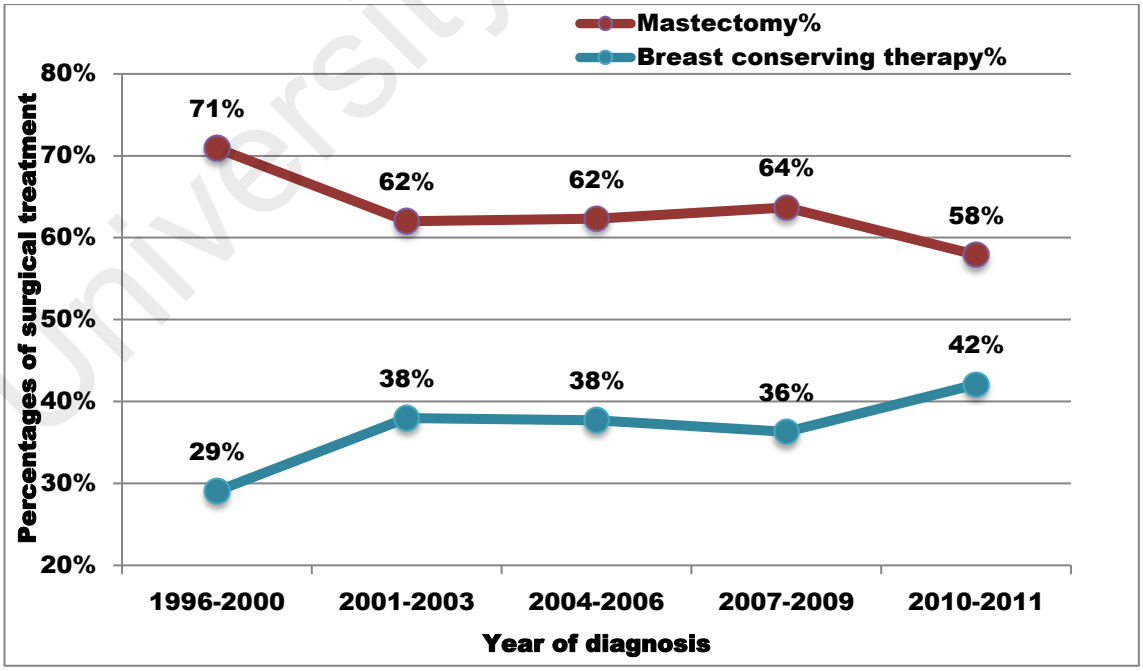

Figure 4.4: Proportion of women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line) by age at diagnosis 40-49 years old.

COUNTRY

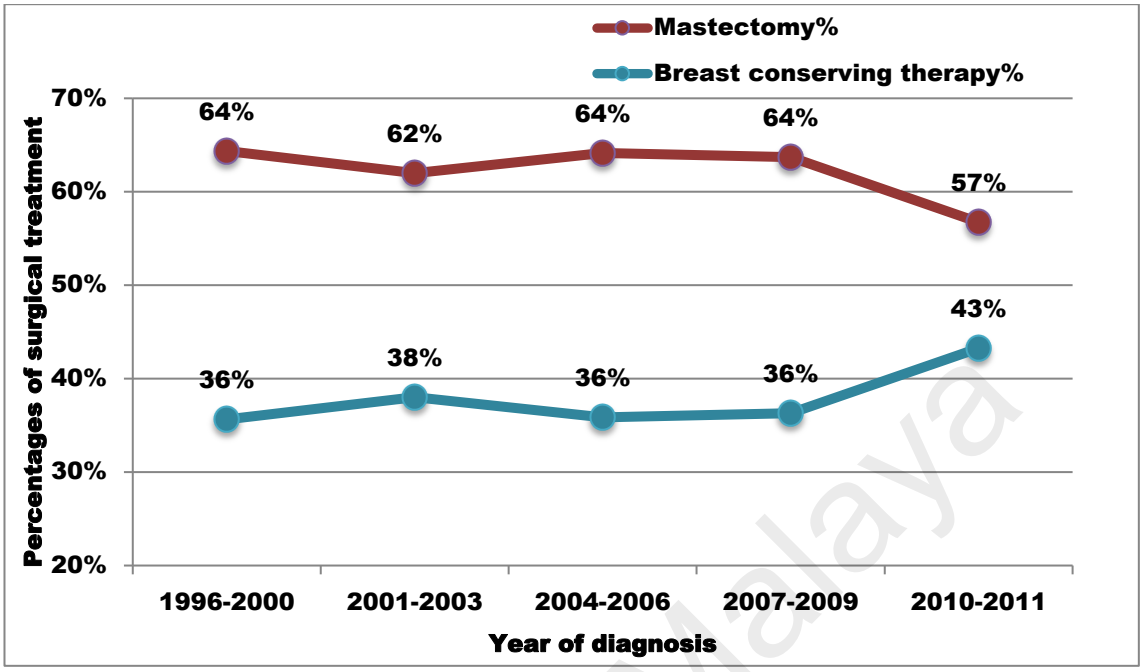

Figure 4.5: Proportion of Malaysian breast cancer patients with early stage of breast cancer undergoing mastectomy (red line) and breast conservation therapy (blue line).

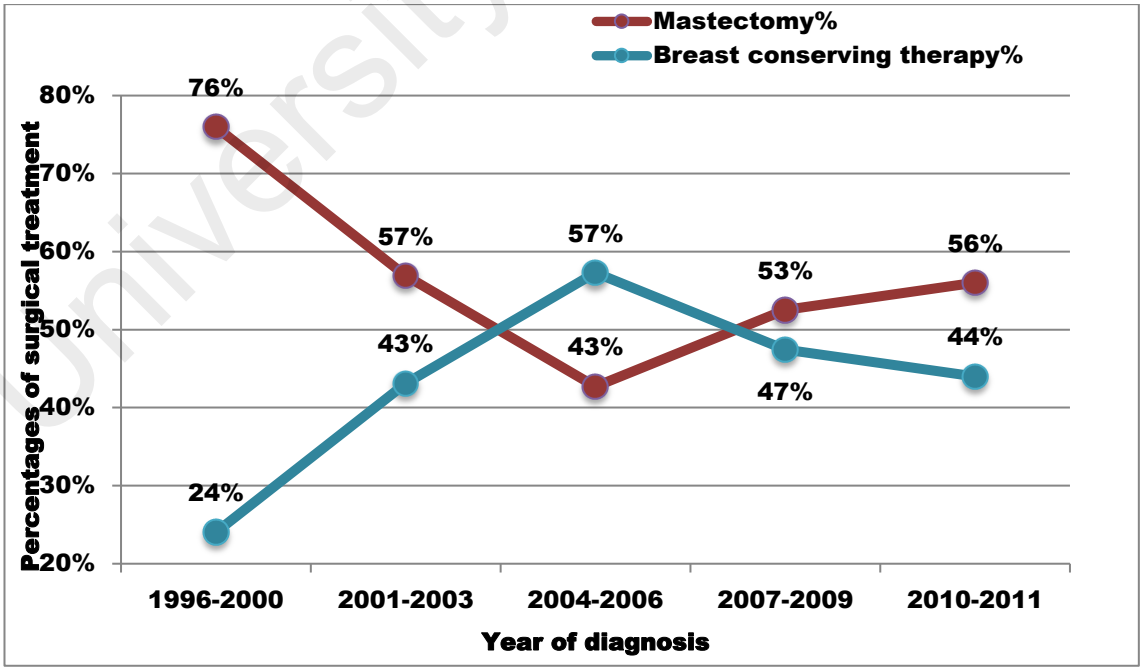

Figure 4.6: Proportion of Singapore's women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line)

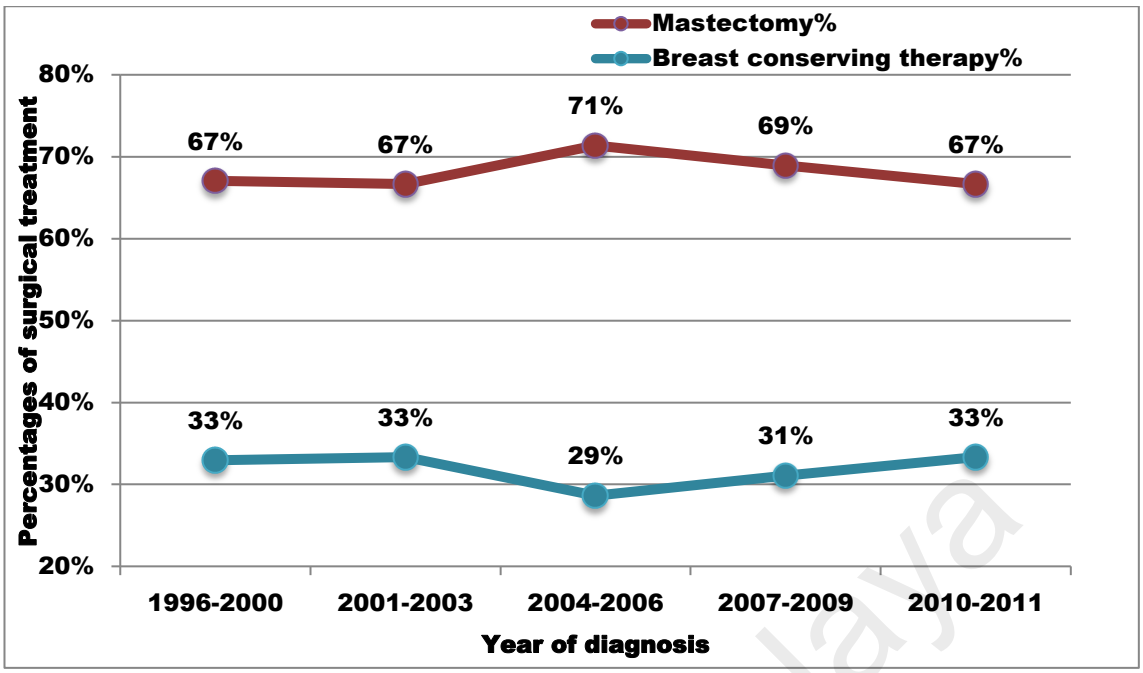

Figure 4.7: Proportion of Hong Kong's women with aerly stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line)

ETHNICITY

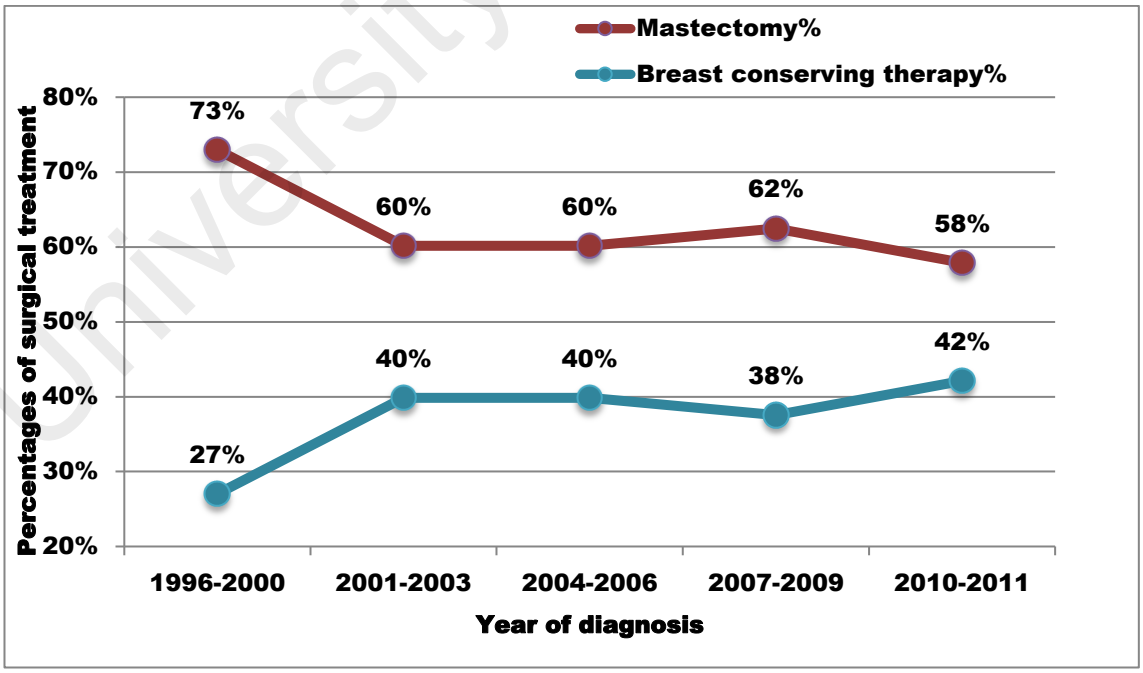

Figure 4.8: Proportion of Chinese women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line) by ethnicity.

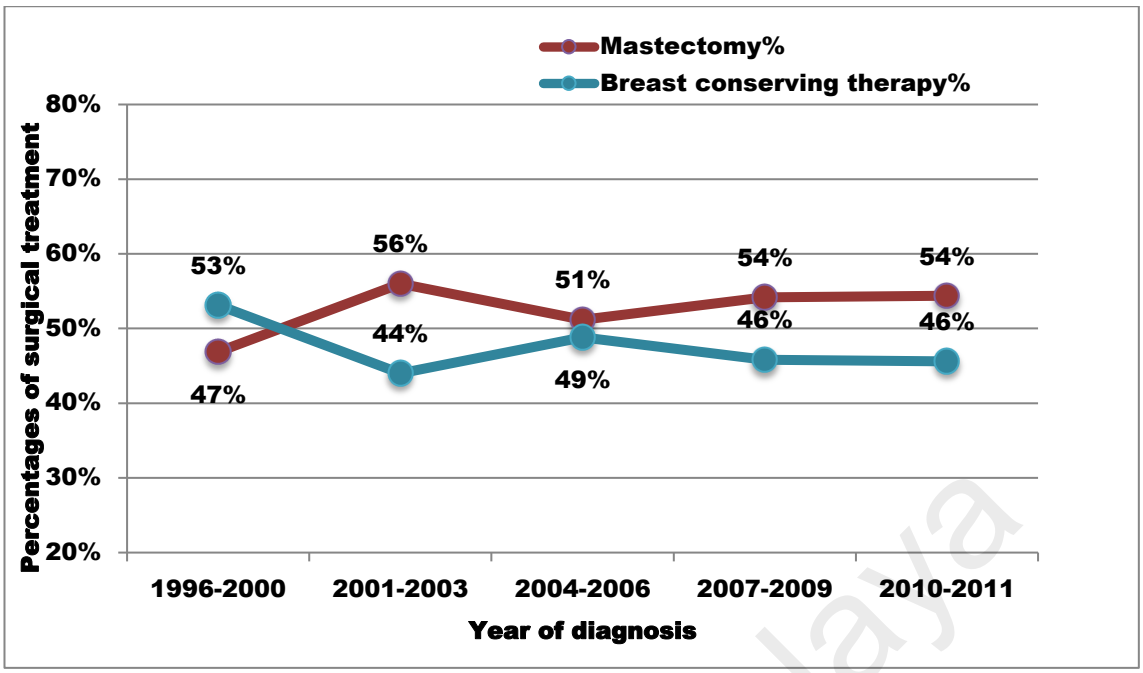

Figure 4.9: Proportion of Malay women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line) by ethnicity.

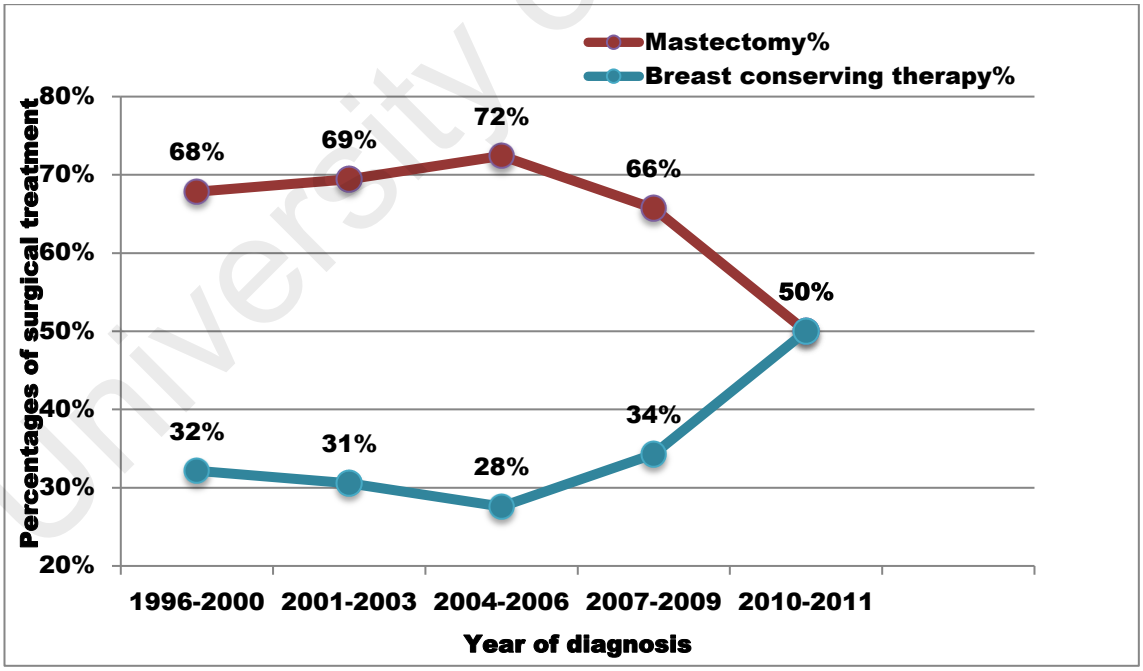

Figure 4.10: Proportion of Indian women with early stage of breast cancer underwent mastectomy (red line) and breast conservation therapy (blue line) by ethnicity.

CHAPTER 5: DISCUSSION

5.1 Summary of main finding

While we observed an increase in BCT rates over time in young breast cancer patients with early stage breast cancer in the Asian settings, there were marked differences in trends of BCT between Malaysia, Singapore, and Hong Kong. Nevertheless, the overall mastectomy rates in early stage breast cancers remained high in these Asian settings. There also appears to be no significant overall survival difference between young patients with early stage breast cancer receiving BCT or mastectomy.

5.2 Findings in context with the literature

It is known that the primary treatment for early stage breast cancer has shifted to a less invasive surgical approach over the past two decades. In the mid-1980s, several randomized trials had documented that BCS with radiation provided similar survival benefit as a mastectomy in treating early stage breast cancer (Fisher et al., 2002; Jatoi & Proschan, 2005; Umberto Veronesi et al., 2002). Apart from it, BCT was associated with a better physical function, sexual function, and body image immediately after treatment, which improved social function and global quality of life (Goss et al., 2003) compared with mastectomy which was associated with an overall poorer quality of life. As such, choice of surgical options may be very impactful for women especially in younger breast cancer patients, since these women may have young children, a desire to conceive,

planning to get married in future and may be in the middle stage of their career life compared to older patients. Following the National Institutes of Health (NIH) Consensus Development Conference in 1990, BCS with the radiation have been established as an appropriate primary therapy for women with stage I or stage II breast cancer ("Consensus statement: treatment of early-stage breast cancer. National Institutes of Health Consensus Development Panel," 1992). Thus, breast conserving surgery has replaced mastectomy as standard of care for early stage breast cancer patients. Breast conserving surgery or "Lumpectomy" with radiation is considered a less invasive surgical approach as it preserves the breast and reduce the issues of body image concern, sexual function problems, and other psychosocial factors after surgery (Levy, Herberman, Lee, Lippman, & d'Angelo, 1989; Schain & Fetting).

Apart from our present findings, several other studies have also demonstrated equivalent survival outcomes for patients with early stage invasive breast cancer treated by breast conserving therapy or mastectomy (Rodrigo Arriagada, Lê, Rochard, & Contesso, 1996; M. Blichert-Toft et al., 2008; Cao, Olson, & Tyldesley, 2013; Coulombe et al., 2007; Lichter et al., 1992; Mahmood et al., 2012; Umberto Veronesi et al., 2002). Nevertheless, the value of BCS in young patients had remained controversial issue because of the notion that breast cancer in young patients tends to be more aggressive and to present at more advanced stages (Barlow et al., 2001). Several reports revealed that BCS in young patients was associated with increased loco-regional recurrences (Clarke et al., 2005; Feigenberg et al., 1977; Fisher, 1977; B. I. G.-C. Group, 2005; S.-E. Lim et al., 2007b; A. C. Voogd et al., 2001). Some studies even showed that young women have inferior cosmetic outcomes with BCS and at high risk of local recurrences, implying that such women may be better off receiving mastectomy (Fisher et al., 1985; A. C. Voogd et

al., 2001). On the other hand, there are studies indicating breast cancer in young women can be managed with safely with breast conserving therapy with better prognosis (S. Agarwal et al., 2014; Coates et al., 2007; Fisher et al., 2002). The survival advantage associated with BCT might be due to the lack of adjustment for potential confounders, unmeasured confounding factors(patients or physicians selection), as well as the effect of confounding by indication arising from tendency for patients with more favourable prognostic factors such us smaller, and less aggressive breast tumours to be subjected to BCT. In the current study, we had comprehensive information on breast cancer tumours profile and treatment characteristics of the patients, which allowed us to adjust for these factors by using propensity scores, hence minimizing the above biases.

Our findings on survival outcomes between mastectomy and BCT were in line with the report summarized following the 1990 National Institutes of Health Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma and Breast Cancer Specialist (EUSOMA) working group that, breast conserving therapy is recommended as a standard treatment of care for early stage breast cancer patients as it provides similar survival outcomes as mastectomy (Lazovich et al., 1999; L. Y. Lim et al., 2017).

The current study also demonstrates that a high proportion of patients with stage I and stage II breast cancer in this Asian setting were treated with mastectomy (64%) and only (36%) of patients were treated with BCT. Despite high proportion of patients undergoing mastectomy, there seems to be a tendency towards increasing BCT rates; overall proportion of women with early stage breast cancer who are receiving BCT increased

marginally from 33% in 1996 to 40% in 2011, representing the trends in surgical option towards BCT in this Asian settings. We discuss the results cautiously taking into account of different age groups, countries and ethnicities. The present retrospective study confirmed that increasing BCT rates from 1996 to 2011 was noticed in nearly all patients but were most pronounced among young group 40-49 years old, which is 29% to 42% compared to very young group 20-39 years (37% to 39%). Our trend results showed that younger breast cancer patients, 20-39 years old were more likely to receive mastectomy compared BCT. Notably, the panel of the 2013 St.Gallen Consensus had suggested that young age in itself is not an absolute contradiction for breast conserving-surgery (E. Y. Tan et al., 2005), even though young age is known as an establish risk factor for poorer prognosis after the diagnosis of breast cancer (Theriault et al., 2013). A randomized controlled trial by the Danish Breast Cancer Cooperative Group (DBCG), had reported that younger patients were more likely to receive BCT (*p<0.01)* (Smigal et al., 2006). This study further revealed that those who received BCT had a 5.2-fold higher incidence of recurrence in the breast within period of 5 years among women aged < 35 years compared with women aged 45 to 49 years (15% vs. 3%, respectively). However, no differences in risk of mortality was shown between women subjected to BCT and mastectomy, regardless of age. A vast majority of previous retrospective studies in early stage breast cancer patients have also failed to show a clear survival benefit in support of mastectomy as compared with BCT (Barlow et al., 2001; Feigenberg et al., 1977). A very recent population-based study using the Netherlands Cancer Registry in fact showed that in women diagnosed with stage T1-2, N0-1, M0 breast cancer, BCT was associated with improved 10 years overall survival (adjusted HR 0·81 [0·78-0·85]) and relative survival (adjusted HR: 0·76 [0·64-0·91]), compared with mastectomy. Albeit concerns of confounding by indication in this observational study, its results at the least suggest that BCT is equivalent to mastectomy with respect to overall survival, and should be the

recommended mode of surgery in all eligible breast cancer patients (Coates et al., 2007).

Despite the lack of strong evidence suggesting the superiority of mastectomy in early stage breast cancer, an increased trend has been observed in our study for young patients aged 20-39 to undergo mastectomy instead of BCT. Similarly, one National Cancer Data Base study showed that, from 2003 to 2010, BCT in patients aged ≤ 45 years decreased from 61.4% to 49.4% and bilateral mastectomy increased from 9.3% to 24.1% (E. B. C. T. C. Group, 2005). Two other reviews of National Cancer Data Base have reported that amidst the setting of an overall increase in BCT, younger women with breast cancer are being treated with mastectomy at higher rates than their older counterparts after adjusting for patient, facility, and tumour characteristics (Freedman et al., 2012; Lautner et al., 2015). Women aged ≤ 35 years was noticed nearly two-fold of young breast cancer patients likely to receive mastectomy compared to women aged 61-64 years.-The concern on locoregional recurrence and fear of taking additional treatment were possible reason young women prefer to receive mastectomy. Barriers to receiving radiation might be one of the reason why young women tend to receive mastectomy instead of BCT. This is due to the accessibility and time commitments, which present major barriers to receiving radiation. The current commonly used breast radiation method after breast-conserving surgery in young patients is given daily, 5 days a week, for up to 6 to 7 weeks. Given that patients are required to have regular visits to complete the therapy, it may cause significant disruptions in daily activities (E. B. C. T. C. Group, 2005). As young breast cancer patients are confronted by unique challenges such as still having young dependent children and being in mid-stage of their career life. Finding from a study of women aged 20 to 64 years who had underwent breast- conserving surgery showed that nearly 15% did not receive adjuvant therapy (Huang et al., 2017). The important reason associated

with failure to receive adjuvant radiation therapy was having ≥ 1 children with age less than 7 years old, and this association was driven primarily by young women aged 20 to 50 years. In addition to above, it has been hypothesized that the molecular and genetic characteristics of breast cancer that arise in younger women, such as BRCA mutations, may be different from that of older women. A study of women diagnosed with breast cancer before the age of 46 years in Spain showed the frequency of BRCA mutations in cases diagnosed before age 40 is higher (Henry et al., 2016). Two other studies conducted in United Kingdom also reported that the proportion of breast cancer patients with BRCA1 and BRCA2 mutations is higher in women less than 36 years of age compared to their older counterparts (6% vs. 3%) (Henry et al., 2016). Considering the above, suspicion of presence of BRCA mutation in women aged 20-39 may be relatively high that both patients and physicians may unanimously opt for mastectomy instead of BCS. This may not be the case in women aged 40 or more, who might be concerned of body image and sexuality, especially in view of pending menopause and hence accept BCS as a more favourable surgical option.

This finding is also in contrast with Western settings, which have demonstrated evidence of a reversal in the previously decreasing national therapeutic mastectomy rates (Habermann et al., 2010), despite strong evidence of equivalent long term survival for breast conserving surgery and mastectomy, (Rodrigo Arriagada et al., 1996; Fisher et al., 2002). The reversing trends were observed as preponderance towards mastectomy from BCT (Kummerow et al., 2015). The steepest rise in rates of mastectomy in the United States was seen in younger women, who were in fact more eligible for BCT with noninvasive disease, smaller tumor size, and lymph node- negative breast cancer. Although the reasons for increasing rates of mastectomy are not completely understood,

the increase in patients' awareness of family history or hereditary breast carcinoma disorder may also be influencing mastectomy rates in younger women, who are known to be at higher risk for having deleterious genetic mutation. Socioeconomic status, such as ownership of private insurance for immediate reconstruction after mastectomy (Albornoz et al., 2012) and education regarding reconstruction options with excellent outcome are also associated with increased use of mastectomy. The introduction of preoperative breast MRI, (Connors, Goodman, Myckatyn, Margenthaler, & Gehlert, 2016; Garcia-Etienne et al., 2012; Mahmood et al., 2013), patients' concern about recurrence, physician's recommendation, and overestimation of adverse effect of radiation therapy (Hawley et al., 2014; Montgomery et al., 1999) may explain the high rates of mastectomy. Apart from it, young women may opt for mastectomy instead of BCT to lower their subsequent risk of another BC, attain "peace of mind," and the perceived chance of improved survival with more aggressive surgery (E. B. C. T. C. Group, 2005). Furthermore, influence from celebrities and the media may also play a role in increasing mastectomy rates; for instance in the case of Angeline Jolie.

Despite the increasing rates of BCT among young survivors with early breast cancer in this study, our mastectomy rates remain high compared to recent reports from western settings (65% versus 37.9%) (Mahmood et al., 2013) and (65% versus 26.5%) (S. Agarwal et al., 2014). It is known that in some patients, BCT may be contraindicated due to biological or clinical factors such as smaller breasts and a large tumuor-to-breast ratio. (Faermann, Sperber, Schneebaum, & Barsuk, 2014). Multifocality (MF) and multicentricity (MC) are also considered as a relative contraindiction for breast conservation therapy (Network, 2013; Senkus et al., 2013), due to higher risk for breast recurrence, thus radiotherapy may be less effective in the case. Secondly, MF/MC often

results in less favourable cosmetic outcome due to wider excisions and larger boost volumes with more fibrosis (Nijenhuis & Rutgers, 2015). Besides that, some women faces problem in adhering to adjuvant radiotherapy following BCT as there are barriers such as inability to undergo radiation therapy due to logistic issues or under special circumstances such as being pregnant. In addition, patients with strong family history with documented genetic predisposition which is associated with a high risk of second primary breast cancer (Teh et al., 2014) are not advised to undergo BCT as their risk of recurrence are very much higher than those without a family history.

Being Asian may well be an independent predictor of mastectomy. Generally, Asian young women with breast cancer represent a unique entity with more aggressive tumours including higher proportions of intraductal histology and lymphovascular invasion (Bollet et al., 2007) and triple negative breast cancer (Bhikoo, Srinivasa, Yu, Moss, & Hill, 2011). Indeed, in the present study, we observed that unfavourable tumour characteristics were significantly associated with mastectomy. Owing that nearly 70% of our population were from Chinese ethnicity, our high mastectomy rate can be related specifically to physical attributes. Chinese women tend to have smaller volume breast (SVB) tissue compared to other Asian races (Zakariyah et al., 2016) and also Caucasians, which may pose a barrier to BCT (Qiao, Zhou, & Ling, 1997; Yau et al., 2009) leading to greater likelihood of poor cosmetic outcomes in small-breasted women. . Cultural belief and traditional practices may play an important role in surgical choice, such as cultural beliefs about body image, disease and death, beliefs in alternative treatments for breast cancer (i.e. traditional medicine), approaches to medical decision-making, cost of medication and issues with physicians. For instance, certain Asian cultures have fatalistic views with respect to cancer whereby they belief that death is inevitable when cancer is present (Nirmala Bhoo-Pathy et al., 2012). Therefore, Asian patients are more likely to

opt for convenient and less troublesome treatment such as mastectomy. The decision to undergo mastectomy may also arise from the desire to lower the risk of another breast surgery in case of local recurrence, attain "peace of mind", and the perceived chance for improved survival. The Asian culture is a family-oriented one where most women may place importance in the opinion of their partners as well as other family members in making medical decision pertaining to type of surgery. In some instances, patients may also lack the autonomy in treatment related decision-making (Teh et al., 2014). For instance, Chinese culture holds a family-centred model of medical decision-making, where the primary importance is given to family to decide the option of treatment (Nilchaikovit, Hill, & Holland, 1993). It has been postulated that Chinese patients were more wish to prefer mastectomy due to the inconvenience that radiation therapy would burden to family (Kagawa-Singer, Wellisch, & Durvasula, 1997). This behaviour in Asian culture enhances the connection among family members, who feels responsible for the care of patients in the process of illness and curing. Therefore, family involvement play a keys role in providing of good quality of life care for cancer patients in Asian setting (Daher, 2012). Besides the above, modesty and low self-esteem might stop most Asian women from involving fully in decision-making of breast cancer treatment (Mo, 1992; Tang, Solomon, & McCracken, 2000). The misconception that mastectomy eliminates breast cancer completely, and that aggressive surgical treatment would be the best solution to overcome an aggressive disease may further explain the high rates of mastectomy in Asian settings (M. M. Lee, 2002; Wong et al., 2008). Also, the breast is not as important in the perception of body image in some Asian cultures as in Western cultures (Kagawa-Singer et al., 1997). As a result, concerns about the cosmetics results of surgery my not play a prominent role in influencing treatment choices. Nevertheless, it remains possible that some patients may have undergone mastectomy for financial reasons, to avoid the complications of adjuvant radiation therapy, or due to their small

breast sizes (Bhoo-Pathy et al, 2014). For instance, a woman from low-income background may be unwilling to take length of time off work to just undergo radiotherapy treatment which needed a week as part of complete BCT. Nevertheless, a study using a large health maintenance organization data has highlighted that BCT may associated with higher short term costs but lower long term costs compared to mastectomy (Barlow et al., 2001). However, in Asian countries the study on the cost associated with mastectomy and BCT is minimally studied due to some reasons such as establishment and maintenance of data registries (Anderson et al., 2011). Therefore, it is difficult to draw a conclusion and further research is highly needed in this area. . Also due to logistic reasons, some patients may find RT too cumbersome as they have to have more hospital visits (Huang et al., 2017; B. D. Leong, Chuah, Kumar, & Yip, 2007). While a lack of radiation facilities may explain the high rates of mastectomy in resource limited settings such as in Asia, this is unlikely to explain the low rate of BCT in the present study. This is in view that all four hospitals included in this study were tertiary oncology centres with modern radiotherapy facilities.

Interestingly, a marked regional variation was observed in mastectomy and breast conserving therapy rates in current study. Rates of breast conserving therapy were highest in Singapore compared to Hong Kong and Malaysia. This regional variation has been described in western study using the National Cancer Data Base (NCDB), which highlighted a significant association between geographic region and initial treatment of breast cancer. Similarly, our study showed differences among countries, the highest rate of breast conserving therapy was observed in Singapore and lowest rate in Hong Kong. It appears that as a modern developed country, Singapore had adopted the recommendation of the NIH Consensus Development Conference in 1990, whereby BCS

become the preferred option in Singaporean breast cancer patients with early stage disease; a 20% increase in breast conserving therapy rates were observed from 1996 to 2011. In this well developed and high resource country, the increased rates of BCT may be influence by a well-established cancer care system with sufficient resources, highly organized breast cancer awareness campaigns and a national breast cancer screening program which enable detection of breast cancer at earlier stages for better treatment and survival outcomes. Our finding however is in contrast with another retrospective review performed in 2244 women who underwent curative surgery for non-metastatic breast cancer from 2001 to 2010, in Singapore, which reported an increased rate of mastectomy (P. M. Y. Chan et al., 2015) . This may be due to differences in patient's characteristics, where patients included in current study were young (age <50 years) whereas the previous study included patients age ranging from 23 to 94 years old. The older women in the previous study may have opted for mastectomy in the quest for a shorter treatment course and avoidance of radiotherapy (P. M. Y. Chan et al., 2015). In Malaysia, only a very modest increase in proportion of BCT among early stage breast cancer patients was observed over a 15 year period. We observed that Malay patients were significantly associated with high proportion of BCT compared to Chinese and Indian patients. It is unknown whether this was a preference on the part of the patient or surgeon but based on our experience, difference in culture and belief among Asian women may reflects the increases of BCT. Generally, Asian culture is family-oriented and more reserved, where patients are less involved in decision-making. A study conducted in Malaysia reported that, Malays and Indian patients more prioritized the opinions of partners and family members and were more worried on their loss of feminity compared to Chinese women (Teh et al., 2014). Notably, Malay and Indian women are from more traditional-orientated societies who tend to lack of individualistic and autonomous in decision-making and are more likely to play the role of dutiful wife and daughter, and accept the opinions of

partner and family members (Teh et al., 2014), compared to their Chinese counterparts..

In Hong Kong, we observed the lowest proportion of early stage breast cancer patients (33%) receiving BCT and the more strikingly, the low trends of BCT remained unchanged from 1996 to 2011. Although, Hong Kong is a high resource country with state-of-the-art cancer treatment facilities, BCT uptake in early breast cancer was very low. It has to be noted that all the patients from Hong Kong were of Chinese ethnicity, who have been well documented to prefer mastectomy compared to BCT even when having early stage breast cancer. Besides, two other studies on Asian women residing in Western countries showed that only 20%-30% of Chinese patients with early breast cancer received BCT (Gomez et al., 2010; Morris, Cohen, Schlag, & Wright, 2000). It has to be however noted that a study conducted in a single breast center in Hong Kong, examining impact of surgery on quality of life in Chinese women had reported that breast cancer patients receiving BCS had significantly better body image scores as well as other psychosocial outcomes compared to those of receiving mastectomy (Fung, Lau, Fielding, Or, & Yip, 2001). Despite the advantages of breast conservation treatment on quality of life and provision of similar survival benefit as mastectomy, patients from Hong Kong tend to have more mastectomies. An important potential explanations for high mastectomy rates in Hong Kong, is the relatively small breast size of Chinese women, making BCT unsuitable for most patients (Yau et al., 2009). Apart from the explanations given above, this may also be attributed to over-estimation of survival benefits paired with expectation of lower complications from mastectomy (Yau et al., 2009).

Importantly, our study suggest that there is no difference in survival outcomes

following mastectomy or breast conservative therapy in early stage young breast cancer patients in Asian settings. Our results were compatible with previous finding (M. Blichert-Toft et al., 2008; Cao et al., 2013; Coulombe et al., 2007; Mahmood et al., 2012), which demonstrate similar survival outcome between BCT and mastectomy. We also performed subgroup analyses for triple negative breast cancer (TNBC) patients to find whether type of surgery impacted their survival. The analysis by TNBC subtype of surgery at 10 years suggested a great improvement in locoregional therapy for the young women treated with BCT, but this was not statistically significant and did not translate into better overall survival compared to mastectomy. Although this great difference is statistically insignificant, the comparison is performed using the small sample size, which limits our ability to make a definitive conclusion. Moreover, previous studies (Bhoo-Pathy et al., 2015; O'Rorke, Murray, Brand, & Bhoo-Pathy, 2016) have reported that adjuvant radiotherapy may be independently associated with both locoregional and overall survival gain in young patients with triple negative breast cancer. Considering the above, it remains possible that breast preserving surgery plus radiotherapy may yield a better survival outcome in young TNBC patients.

From the patient's perspective, BCT may be associated with substantial advantages compared to mastectomy, as BCT helps to maintain or restore quality of life, preserve self-image, and positively impact sexuality (Lazovich et al., 1999). Taken together with our finding that there is no survival difference between those undergoing BCT and mastectomy, more efforts need to be taken in Asian settings to educate patients and physicians, likewise to opt for BCT as the treatment of choice in young breast cancer patients with stage I or stage II disease. Nevertheless, any recommendations in support of breast conserving surgery must be made taking into consideration bearing in mind that all

women planned for BCS must have access to adjuvant radiotherapy. To our knowledge, this the first study investigating overall survival of breast conserving therapy versus mastectomy using multi-ethnic database in collaboration with Malaysia, Hong Kong and Singapore. This international collaborative study provides an insight into surgical patterns following breast cancer in Asian settings which may be generalized in other multiethnic population.

5.3 Limitations and strengths

It is however acknowledged that this study suffer from some limitations such as lack of data on local recurrence which is an important clinical endpoint. Furthermore, we are unsure of the extent of sociocultural factors including poor patients-provider communications and cultural factors that may have contributed to high mastectomy rates in our setting. This is due to lack of information on the above aspects. Although the present study is limited by hospital-based and not population-based data, it benefits from the large number of patients with a broad range of demographic factors, and hence may be considered, representative of the Asian experience. Propensity score analysis was applied in this study to control for non-random treatment assignment of patients by adjusting for differences in covariates between the treatments.

This study has captured some important clinical implications, which may be very useful for clinical practice. Although younger age is a known poor prognostic factor for breast cancer, the available evidence has shown no survival advantage associated with mastectomy over BCT. Therefore, clinicians must continue to educate eligible breast

cancer patients about the risks and benefits of BCT and provide evidence-based recommendations to enable patients to make informed decisions concerning their surgical management.

CHAPTER 6: CONCLUSION

In conclusion, our study using the hospital based breast cancer registries of multiple institutions from Malaysia, Singapore and Hong Kong demonstrated that there are no significant differences in survival outcomes among young women with early-stage breast cancer undergoing BCT or mastectomy. While we observed a modest increase in BCT rates over a fifteen year period, the mastectomy rates in early stage breast cancer patients remain high in Asian settings. Asian breast cancer patients should be empowered with better knowledge on treatment modalities such as BCS and the value of adjuvant radiotherapy. This can be done by organizing more health care or breast cancer awareness campaign, public forum regarding the breast cancer and other activities related to the breast cancer awareness. This will not only address the misperception in some women that mastectomy will yield improved survival following early breast cancers, but also allow all patients to make informed surgical decision-making. Besides, surgeons also has to take into account the patients demographic background such as ethnicity, age, marital status, reliance on partner and family members when counseling on surgical options. Decision making on surgical option is usually a joint effort rather than between the patient and surgeon, bringing the patient's family into the process early is important. Finally, more research on potential reasons for preferring mastectomy versus BCT, should be further investigate in future research across different areas of the country.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

Conference presentation (Oral):

Siamala Sinnadurai, Maznah Dahlui, Nur Aishah Taib, Nirmala Bhoo Pathy (2015, November). Breast conserving therapy versus mastectomy in young breast cancer patients in Asian Settings. *Kuala Lumpur Symposium on ASEAN University Ntework (AUN)- Kyoto University (KU), November 23rd -24th , 2015, at Institute of Graduate Studies, University Malaya, Kuala Lumpur, Malaysia***.**