

1.0 INTRODUCTION

1.1 Epidemiology

Breast cancer is the most common cancer in women in Malaysia. The third issue of the National Cancer Registry on cancer incidence in Peninsular Malaysia 2003-2005 reported 11,952 new cases of breast cancer. This accounted for 31.3% of newly diagnosed cancers in women. The age-standardised rate for females was 47.4 per 100,000 women. Breast cancer was also the most common cancer in all ethnic and age groups in females from the age of 15 years. The peak age specific incidence rate was in the 50-60 years age group. Chinese women had the highest incidence with 59.9 per 100,000 population followed by Indian women and Malay women with 54.2 per 100,000 and 34.9 per 100,000 population respectively.¹

Breast cancer is also the most frequent cancer in women worldwide. It accounts for 23% of all cancers. With an estimated number of 1.15 million new cases in 2002, it ranked second overall when both sexes were considered together. More than half of the cases were in industrialised countries, about 361,000 in Europe and 230,000 in North America which accounted for 27.3% and 31.3% respectively. Incidence rates were high in most of the developed areas except for Japan, where it was third after colorectal and stomach cancers. The highest age-standardised incidence was in North America at 99.4 per 100,000. The incidence was more modest in Eastern Europe, South America, Southern Africa, and Western Asia, but it was still the most common cancer in women in these geographic regions. The rates were low at less than 30 per 100,000 in most of Africa and Asia. The lowest incidence was in Central Africa.²

The incidence of breast cancer continues to show an increasing trend worldwide. This may be due to the increase in risk factors such as decreased childbearing and breast feeding, increased exogenous hormone exposure and detrimental dietary and lifestyle changes, including obesity and less physical activity.³ In the more developed countries, the increasing incidence may also be explained by the introduction of screening programmes. Screening may detect early cancers, some of which would otherwise have been diagnosed later or not at all.

Despite the increasing incidence, survival has steadily improved over the recent decades. This may be explained by the development of improved treatment modalities and earlier detection due to screening programmes and increased awareness of breast cancer among women. However, breast cancer remains as the leading cause of death in women worldwide.⁴

1.2 Treatment of Non-metastatic Invasive Breast Cancer in University Malaya

Medical Centre (UMMC)

The Clinical Oncology Unit of UMMC started its operation in November 1997 with radiotherapy service only. It was not until a few months later when the chemotherapy daycare service was started, offering chemotherapy treatment to cancer patients.

The treatment of breast cancer was evidence-based and later guided by the Ministry of Health Clinical Practice Guidelines on 'Management of Breast Cancer' which was issued in December 2002. This gives guidance on management of breast cancer from the onset of diagnosis right through to the treatment, follow-up and management of side effects.⁵

The management of patients with breast cancer in UMMC involves a multidisciplinary team which includes breast surgeons, clinical oncologists, pathologists, radiologists and other

support teams. The aim of treatment of non-metastatic invasive breast cancer is cure. Therefore, radical treatment should be delivered to this group of patients. The treatment can be divided into treatment of early breast cancer (EBC) and locally advanced breast cancer (LABC).

1.2.1 Treatment of Early Breast Cancer

Early breast cancer includes stage 1 and 2 diseases. The treatment of EBC consists of surgery followed by adjuvant therapy which includes chemotherapy, radiotherapy, endocrine therapy and immunotherapy according to clinicopathological findings and risk factors.

1.2.1 (a) Surgical Treatment

Women with early breast cancer are offered the choice of either breast conservation surgery (BCS) followed by radiotherapy or mastectomy.⁵ A systematic review by EBCTCG in 1995 showed similar outcomes for breast conservation surgery followed by radiotherapy and mastectomy.^{6,7}

After surgery, patients are seen at the breast combined clinic. In this clinic, histopathology reports are reviewed and patients are counseled on the role of adjuvant treatment to reduce the risk of relapse and mortality.

1.2.1 (b) Systemic Treatment

An Oxford Overview showed that adjuvant chemotherapy reduces the risk of relapse and death by 23% and 17% respectively.^{6, 8} It also demonstrated that anthracycline based chemotherapy improves overall survival further by three percent compared to CMF regimen. The addition of taxanes to anthracycline may improve survival further although the evidence has been conflicting. Several randomized controlled trials (RCT) showed significant improvement in disease free survival but only marginal benefit on overall survival.^{9, 10, 11}

The standard chemotherapy regimens used in UMMC in 1999 and 2000 were CMF (cyclophosphamide, methotrexate, fluorouracil), AC (adriamycin, cyclophosphamide), FEC (fluorouracil, epirubicin, cyclophosphamide) and FAC (fluorouracil, adriamycin, cyclophosphamide). Taxane-based regimens were not used as adjuvant treatment at that time.

Following completion of chemotherapy, patients with hormone receptor positive disease are offered endocrine therapy. An overview by EBCTCG showed that 5 years of tamoxifen given to women with ER positive or ER status unknown breast cancer reduces the annual relapse rate by 41%, contralateral breast cancer by 50% and increases overall survival by 5-10%. The benefits were seen in both pre and post-menopausal women.^{6, 8} For post-menopausal women, several RCTs showed improved disease-free survival for adjuvant aromatase inhibitors. However, there is as yet no significant overall survival benefit.^{12, 13, 14, 15} Therefore, tamoxifen for five years remains the standard of care in UMMC patients if they are suitable for endocrine therapy.

Adjuvant trastuzumab or Herceptin is currently indicated in women with HER2 positive breast cancers with high risk of recurrence.^{16, 17} This is following reports from five RCTs confirming significant improvement in disease free survival. However, none of the patients included in this study had trastuzumab as part of their treatment as evidence for it was only available from 2005 onwards.

1.2.1 (c) Radiotherapy (RT)

A meta-analysis of 40 randomized controlled trials which involved 20,000 women has shown that post-operative radiotherapy after BCS and mastectomy reduces the risk of local recurrence by two thirds. The magnitude of benefit was more in node positive patients, with an

absolute survival benefit of eight percent in node positive and four percent in node negative patients.^{6,7}

Adjuvant radiotherapy is recommended to all patients after BCS as it significantly reduces the risk of local recurrence. Chest wall irradiation after mastectomy is recommended for women at high risk of local relapse.⁵ The role of supraclavicular fossa (SCF) radiotherapy post-axillary dissection is controversial. There are no randomized studies done addressing this issue. A retrospective analysis suggests high rates of recurrences for patients with more than four positive axillary nodes, but there is no data on the impact of SCF irradiation on survival. In UMMC, patients with one to three positive nodes are offered radiotherapy to the chest wall and those with four or more positive nodes are offered radiotherapy to both chest wall and supraclavicular fossa (SCF).

1.2.2 Treatment of Locally Advanced Breast Cancer

Locally advanced breast cancer consists of stage 3 disease. Multimodality treatment using a combination of surgery, chemotherapy, radiotherapy and hormonal therapy is the choice of treatment for locally advanced breast cancers.^{5,18}

In Stage 3 operable cancer, the treatment options are either surgery followed by adjuvant therapy or neoadjuvant chemotherapy followed by surgery. There was no significant difference in outcome between the two treatment strategies, as demonstrated by the NSABP B-18 trial.¹⁹

In Stage 3 inoperable cancer, the treatment of choice is neoadjuvant chemotherapy followed by surgery for patients with good response to chemotherapy. Patients who remain inoperable after chemotherapy may be given radiotherapy.^{5,18} Chemotherapy regimens used for neoadjuvant treatment in this study were FAC, FEC or CMF. In patients who have progressive disease despite neoadjuvant chemotherapy, treatments are individualised depending on the

patients circumstances. Neoadjuvant endocrine therapy may be considered in less fit or older patients with endocrine sensitive disease who are unlikely to tolerate chemotherapy.⁶

The decision on adjuvant radiotherapy after surgery is individualised according to pre-chemotherapy disease status and post chemotherapy clinicopathological factors. In patients with radiological complete response after neoadjuvant chemotherapy, radiotherapy may be used instead of surgery but it is associated with higher local relapse rate. There is lack of evidence on whether surgery or radiotherapy should be offered to patients with complete radiological or clinical response.⁶

1.2.3 Follow-Up

After completing radical treatment, patients are kept under follow-up to monitor for relapse and late side effects of treatment. They are seen in clinics every three months for the first two years, six monthly for another three years and annually thereafter. Surveillance mammogram or ultrasound scan of the breast is carried out annually.

1.3 Breast Cancer Relapse

Non-metastatic invasive breast cancer has the tendency to relapse even after adequate curative treatment. The sites and the timing of relapse are important determinants of outcome in patients with relapsed breast cancer.

Sites of relapse can be divided into local, regional and distant. They play a significant role in the management decision. Patients with local and regional relapse may still be suitable for curative treatment, whereas in patients with distant relapse the aim of treatment is usually

palliative. The risk of relapse may be estimated based on clinical and pathological risk factors. Due to this risk, patients are followed-up long term after completing all curative treatment.

Currently, we do not have any published data on the patterns of breast cancer relapse in Malaysia. Therefore, this study was performed to analyse the patterns of breast cancer relapse and the prognosis following relapse.