CLINICAL PRACTICE GUIDELINES

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MANAGEMENT OF BREAST CANCER

MINISTRY OF HEALTH MALAYSIA   **ACADEMY OF MEDICINE**

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in December 2002 and will be reviewed in December 2004 or sooner if new evidence becomes available

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GUIDELINE DEVELOPMENT AND OBJECTIVES

Guideline Development

Currently, there is a marked variation in the diagnosis and management of breast cancer. The probable reason can be attributed to the fact that the disease has many and various presentations at different stages of its natural history. As consumer interest increases there is a need to standardize the management in order to improve the quality of health care given to breast cancer patients.

The clinical practice guidelines on 'Management of Breast Cancer' was prepared by a committee comprising of surgeons, pathologist, radiologist, oncologist, public health care physicians and a palliative care specialist from the public and private sectors using a standard methodology based on a systematic review of evidence.

Objectives

The aim of the guideline is to present evidence based recommendations to assist the healthcare professional in clinical decision making by providing well balanced information on how to arrive at a diagnosis of cancer without undue delay, achieve both local and systematic control of disease by a multidisciplinary approach with reduction of the risk of recurrence to improve survival and maintain a good quality of life for the patient.

Clinical Question

The clinical questions of these guidelines are:
- i) How can breast cancer be diagnosed?
- ii) How can patients with breast cancer be managed successfully?
- iii) What is the management of specific groups of patients with breast cancer?
- iv) Is there a role for screening?
- v) Can cancer breast be prevented?

Target Population

These guidelines are to be applied to women at risk and to women who are diagnosed with breast cancer.

Target Group

These guidelines are developed for all health care professionals involved in the screening and management of breast cancer.

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LEVELS OF EVIDENCE SCALE

(Source: USA/Canadian Preventive Services Task Force)

I   Evidence obtained from at least one properly randomized controlled trial

II-1   Evidence obtained from well-designed controlled trials without randomization

II-2   Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

II-3   Evidence obtained from multiple time-series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence

III   Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

Guidelines	Level of Evidence	References
Women presenting with a breast mass should undergo bilateral mammography if 35 years and above or breast ultrasound if younger, followed by fine needle aspiration cytology or core needle biopsy. If doubt remains as to whether a lump is benign or malignant, an excisional biopsy should be carried out.	Level II-3	Donegan, Pruthi, Edeiken, Grant, Lesnick, Minkowitz
The recommended baseline investigations include a full blood count, liver function tests, and chest X-ray. In patients with clinically Stage 3 and 4 breast cancer, a bone scan and liver CT /ultrasound should be done.	Level III	Baseline staging tests in primary breast cancer, Brar, Cox
Counselling is recommended for women with breast cancer, as it improves quality of life	Level 1	Devine
Where appropriate, women with early breast cancer should be offered a choice of either breast conservation surgery followed by radiotherapy or mastectomy, as there is no difference in the rate of survival.	Level I	Veronesi, Fisher, Morris, Voogdt
Immediate breast reconstruction should be offered to women undergoing mastectomy, wherever possible, as it will not affect long-term outcome of the disease	Level II-1	O'Brien, Nho, Beckenstein
Removal and pathological examination of axillary lymph nodes (at least Level I or II) should be standard procedure for patients with early invasive cancer.	Level 1	Recht, Whitworth, Cabanes, Davies
Radiotherapy after breast conservation surgery is recommended as it significantly reduces the risk of local recurrence.	Level I	Fisher 1989, Fisher 1995
Chest wall irradiation after mastectomy is recommended for women at high risk of local relapse.	Level I	Overgaad 1997, Overgaad 1999 Ragaz
Adjuvant multi-agent chemotherapy reduces the risk of recurrence and death for women with breast cancer. It should be offered to all patients in the high-risk category i.e. all node positive patients, node negative patients with tumours 2 cm or more, or ER negative. It may be considered in women with moderate risk of recurrence, ie1-2 cm, Grade 3 or lymphovascular invasion.	Level I	Polychemotherapy for early breast cancer 1998, 2001, Hortobagyi, NCCN guidelines,St Gallen guidelines

Guidelines	Level of Evidence	References
Adjuvant tamoxifen for 5 years is recommended for women with ER positive tumours as it significantly improved recurrence-free and overall survival.	Level I	Tamoxifen for early breast cancer 1998
Women should be informed of the small risk of endometrial carcinoma with tamoxifen.	Level I	Bergmen
If appropriate, ductal carcinoma in situ can be treated with breast conservation surgery followed by radiotherapy. Mastectomy is required in the presence of diffuse disease.	Level I	Fonseca, Wright, Van Zee Bradley, Fisher 1993
Axillary surgery is not usually performed in a women with ductal carcinoma in situ.	Level III	Bradley, Bijker
Multimodality treatment with a combination of chemotherapy, surgery, radiotherapy and hormone therapy (in ER positive patients) is the treatment of choice for locally advanced breast cancer (Stage 3)	Level II-2	NCCN guidelines Willsher, Hortobagyi 1999
A minimal follow-up schedule is recommended as there is no evidence that frequent intensive follow-up with blood tests and imaging confers any survival benefit or improvement in quality of life.	Level I	Temple Del Turco, Grunfield
In metastatic breast cancer, the aim of treatment is to palliate symptoms and maintain the best quality of life	Level III	Ellis MJ
In metastatic breast cancer, the choice of chemotherapy, hormone therapy or immunotherapy should be individualized	Level III	NCCN guidelines
In terminal breast cancer, proper palliative specialist care improves patient outcome in relation to patient satisfaction family satisfaction, pain control and control of symptoms and anxiety.	Level I	Hearn J
Breast cancer in a pregnant woman should be managed in the same way as a non-pregnant patient, except that radiotherapy is contraindicated. Breast conservation surgery is contraindicated and mastectomy and axillary dissection should be carried out without delay. Chemotherapy can be given in the second and third trimester	Level III	Di Fronzo, Petrek, Kimberley

Guidelines	Level of Evidence	References
The optimal treatment for operable breast cancer in the elderly (>70 years old) is surgery, and tamoxifen alone should be reserved only for the very frail	Level 1	Lickley, Gajdos, Riley, Robertson 1992
In patients with bone metastases, bisphosphonates reduce the incidence of skeletal complications in women with documented lytic lesions	Level I	Lipton, Theriault, Hortobagyi 1996 Hillner
Treatment of spinal cord compression with radiotherapy is as equally effective as surgery in achieving symptomatic relief. If immediate surgery or radiotherapy is not possible, the patient should be started on high-dose steroids (16 mg dexamethasone daily)	Level II-2	Siegal, Posner, Arcangeli, Jeremic Loblaw,, Sorensen
Intravenous bisphosphonate is indicated in patients with malignant hypercalcemia	Level II-1	Purohit
Studies on screening mammography has shown a30% reduction in mortality from breast cancer after 8 years in the screened group; this effect is most marked in the 50-70 year age group	Level I	Nystrom, Roberts, Shapiro, Andersson, Frisell, Heimann
The mammogram report should reflect if the finding is normal, benign or suspicious, and also indicate the further evaluation that may be essential to reach a diagnosis.	Level III	ACR Imaging Reporting and Data System
Complementary and alternative therapies are widely used by breast cancer patients and it is essential that doctors are aware of any alternative therapies the patient may be using, as this may affect the conventional therapy that they are on	Level III	Alternative medicine use worldwide Ernst

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1. INTRODUCTION

1.1. Incidence of Breast Cancer

Breast cancer is the third most common cancer worldwide and is the most common cancer in women. Since 1991, breast cancer has been the second leading cause of cancer admissions in Ministry of Health hospitals, and deaths due to breast cancer is in fourth place in terms of cancer deaths accounting for 6-8% of all cancer deaths.

According to the 1996 report of the Penang Cancer Registry, the breast cancer incidence in Malaysia was estimated at 34.0 per 100,000 population, suggesting at least 3,500 cases annually. Breast cancer was seen to affect mainly women between the ages of 40 and 64 years old, and appeared to be predominant among the Chinese with an age-standardized rate (ASR) of 44.5 per 100,000 population followed by Indians 27.2 per 100,000 population and Malays at 18.1 per 100,000 population. The majority of cancer cases, 44%, are diagnosed at Stage 2 (Penang Cancer Registry).

1.2 Aetiology of Breast Cancer

Several factors have been identified as potentially responsible for increasing breast cancer risk, but their mechanism of action is unclear (McPherson, 2000) (Level III). These factors are:

- Previous history of breast cancer
- Increasing age
- Geographic variation
- Family history
- Biopsy confirmed benign proliferative breast disease
- Previous radiation to the breast
- Nulliparity at age 40 years
- First full-term pregnancy at age of 35 or more
- Early menarche (aged 12 and younger)
- Late menopause (aged 55 and older)
- History of primary cancer of the ovary or endometrium
- Obesity in postmenopausal women
- Evidence of specific genetic susceptibility (such as carriage of BRCA1, BRCA2 or BRCA3)
- Staple diet containing red meat, high total fat (especially saturated fat) and alcohol
- Hormone replacement therapy – the Women's Health Initiative study found an increased risk of breast cancer (Hazard Ratio 1.26) in women on hormone replacement therapy with combined estrogen plus progestin given in a continuous manner (Women's Health Initiative Investigators, 2002)

In a study of population-based series of early-onset breast cancer patients, it was found that approximately 10% of these patients had clearly deleterious mutations in BRCA 1 and BRCA2, and that 15% had BRCA1 and BRCA2 alterations of unknown significance. Although mutations in these genes confer high risk of breast and ovarian cancer, wide

variability in the age at diagnosis and cancer site is observed, even between carriers of the same mutation. (McPherson, 2000; International Agency for Research in Cancer, 2000)

2.   DIAGNOSIS OF BREAST CANCER

2. 1   Clinical Diagnosis

The efficacy of the clinical examination in distinguishing malignant from benign breast lumps depends on the expertise and experience of the examiner (Donegan, 1992). The size, site, mobility, associated skin retraction, erythema, axillary lymphadenopathy or signs and symptoms of metastatic disease are important for clinical staging so as to decide on treatment options (Pruthi 2001).

Women presenting with a breast mass should undergo bilateral diagnostic mammography, and if necessary, an ultrasound examination, before biopsy (Sickles, 1983). Mammography can often clarify the nature of the lump and detect clinically occult lesions in either breast (Edeiken, 1988). In women younger than 35 years, the dense breast tissue lowers the sensitivity and therefore ultrasound directed at the area of concern is the preferred study (Lesnick, 1977).

What is the role of biopsy?

The decision to use core needle biopsy, fine needle aspiration biopsy, or excisional biopsy should be considered in the context of the clinical scenario, taking into account the experience of the physicians concerned. However, the recommended practice is to have a tissue biopsy before open surgery (The palpable breast lump 1998)(Level III).

Fine needle aspiration biopsy has a reported false negative rate of 1%-35% and an overall sensitivity of 94%. Optimal results are obtained with a careful technique, adequate sampling and evaluation by an experienced cytopathologist (Grant, 1986; Rimsten, 1975)(Level II-3).

Core needle biopsy is an alternative to open surgical biopsy, with an overall sensitivity of 89% and a false negative rate ranging from 1.6% to 19%. In larger tumours more than 2.5 cm, the sensitivity increases to 94% (Minkowitz, 1986; Cusick, 1990) (Level II-3).

Whenever reasonable doubt remains as to whether a lump is benign or malignant, open surgical biopsy should be carried out. Excisional biopsy remains the diagnostic gold standard with almost 100% sensitivity (Pruthi, 2001). When surgical biopsy is used, the aim is to remove the whole lump in one piece along with a surrounding cuff of normal tissue. The specimen should be marked with sutures or clips to indicate the orientation (The palpable breast lump, 1998).

2.2   Baseline Staging Investigations

The AJCC (American Joint Committee on Cancer) Cancer Staging Manual (6th Edition) has been used for staging of cancers in this guideline (Appendix 1).

The recommended work-up and staging tests of invasive breast cancer includes a complete blood count, liver function tests, chest radiograph and bilateral mammography. (Baseline staging tests in primary breast cancer: a practice guideline, 2001).

Patients with Stage III and IV breast cancer clinically should undergo a chest X-ray, liver ultrasound or CT scan, and bone scan. In other stages, the performance of a bone scan is not required unless in the presence of bone pains or an elevated alkaline phosphatase (Brar, 1993; Cox, 1992) (Level III).

Additional studies, such as a computed tomography or ultrasound of the liver may be required in patients with abnormal liver function (Brar, 1993; Cox, 1992).

In women with no symptoms, physical signs or biochemical evidence of metastases, the recommendation depends on the pathological stage of the cancer. Therefore routine bone scan and liver imaging are not indicated before surgery. This guideline proposes:

- In women with pathological Stage I tumours, routine bone scan and liver imaging are not indicated
- In women with pathological Stage II tumours, a post-operative bone scan may be considered as part of baseline staging. Routine liver imaging may also be considered for patients with 4 or more positive nodes.
- In women with pathological Stage III tumours, bone scanning and liver imaging are recommended post-operatively.
  (Baseline staging tests in primary breast cancer: a practice guideline, 2001)

However, the decision for a staging bone scan in individual patients may need to be influenced by the availability of resources.

2.3   Laboratory Diagnosis

2.3.1   Invasive carcinoma of the breast

The gross description and sampling should include the following:

General information: type of specimen, weight (biopsy only), dimension and size of specimen in cm
Lesion(s): size of lesion in cm (the breast should be sliced at 1 cm intervals), description of lesions, involvement of the skin.
Surgical margins: whether any margin is grossly involved, distance of lesion(s) from nearest margin. Margins within 2 cm from the lesion must be sampled and all sampled margins must be inked.
Axilla: Number and appearance of lymph nodes (Carter, 1989). Axillary tissue should be sliced at 0.5 cm intervals. Sampling the lymph nodes is optional.
(The pathology reporting of breast cancer, 2001)

The histology should include the following:

The Lesion: size of carcinoma (histological assessment)(Carter 1989), histological type (World Health Organization 1981)(WHO classification), histological grade (Modified Bloom & Richardson system) (Pereira,1995; Elston, 1991), presence and nature of other lesions, presence of carcinoma-in-situ (if present, state what proportion of the mass is in-situ carcinoma, type and nuclear grade); presence of lymphovascular invasion (Pinder, 1994), the status of margins, including distance from nearest margin in cm

Staging: Status of lymph nodes, the number involved/number sampled, extranodal extension, whether nodes are matted (Carter,1989)

Predictive and prognostic factors: oestrogen receptor (ER), (Looi, 1997; Harvey, 1999; Layfield, 2000) progesterone receptor (PR) and oncogene c-erbB-2 status (Venter,1987; Sjogren, 1998; Walker, 2000)

Commonly used definitions are indicated in Appendix 2.

2.3.2   Ductal carcinoma-in-situ (DCIS)

The following characteristics should be recorded for each case of pure carcinoma-in-situ: size (maximum diameter), margins (state distance from nearest margin), nuclear grade (based on criteria by Elston & Ellis), necrosis (whether comedo-necrosis is present or not), architecture (state dominant histological type, whether there is cancerisation of lobules and Pagetoid spread), calcification (state whether present or absent), ER, PR and c-cerbB-2 status (Fisher, 1999; The Consensus Conference Committee, 1997; Silverstein, 1996).

2.3.3   Lobular carcinoma-in-situ (LCIS)

There is a need to specify the presence or absence of lobular carcinoma-in-situ. There are no histological subtypes, and assessment of excision margins is unnecessary, as the process is multi-centric in a high proportion of cases.

3.   MANAGEMENT OF BREAST CANCER

3.1   Counselling

The patient should be counselled adequately once a diagnosis of breast cancer is made, especially about the options of treatment. If she requests a second opinion, she should be allowed to do so, and all relevant reports given to her. Referral should be made early to the local breast cancer support group wherever possible. Studies have shown that counselling and providing patients with support and detailed information about their diagnosis and treatment increases their emotional well-being and assists their physical and emotional recovery (Devine, 1995) (Level I).

3.2   Surgery
3.2.1   The Choice of Operation for Stage I And II

Breast conservation surgery or mastectomy?

Breast conservation surgery (BCS) followed by radiotherapy is an appropriate method of primary therapy for the majority of women with Stage I or II breast cancer, and is preferable because it provides survival equivalent to total mastectomy and axillary clearance while preserving the breast (see Appendix 3 for a review of the evidence). In the absence of special reasons for selecting mastectomy, the choice between BCS and mastectomy can be made according to the patient's circumstances and personal preferences (Veronesi, 1981; Fisher, 1989; Blichert-Toft, 1992; Van Dongen, 1992; Fisher, 1995; "Early breast cancer Trialists" Collaborative Group, 1995; Jacobsen, 1995; Voogdt, et al 2001; Morris, 1997)(Level I).

Mastectomy should be considered in the presence of any of the following:
 (a) factors that increase the risk of local recurrence, such as extensive malignant-type calcifications visible on the mammogram, multiple primary tumours or failure to obtain tumour-free margins.
 (b) physical disabilities that preclude lying flat or abducting the arm, preventing the use of radiotherapy.
 (c) absolute contraindications to radiotherapy such as pregnancy or previous irradiation of the breast or relative contraindications such as systemic lupus erythematosus or scleroderma.
 (d) tumour size of 4 cm or more, or a large tumour size in proportion to breast size.
 (e) the patient's clear preference for mastectomy.
 (f) inavailability of radiotherapy facilities or non-compliance with radiotherapy.
(Veronesi, 1981; Fisher, 1989; Blichert-Toft, 1992; Van Dongen, 1992; Fisher, 1995; "Early breast cancer Trialists" Collaborative Group, 1995; Jacobsen 1995; Voogdt 2001; Morris 1997)(Level III).

The presence of a centrally located tumour mass, axillary lymph node involvement, or the presence of breast implants, are not contraindications for BSC (Veronesi, 1981; Fisher, 1989; Blichert-Toft, 1992; Van Dongen, 1992; Fishe,r 1995; "Early breast cancer Trialists" Collaborative Group, 1995; Jacobsen, 1995; Voogdt, 2001; Morris, 1997).

Before deciding between BCS and mastectomy, the doctor must make a full and balanced presentation to the patient concerning the pros and cons of these procedures (Veronesi, 1981; Fisher, 1989; Blichert-Toft, 1992; Van Dongen, 1992; Fisher 1995; "Early breast cancer Trialists" Collaborative Group, 1995; Jacobsen, 1995; Voogdt, 2001; Morris, 1997).

Whenever an open biopsy is performed on the basis of even modest suspicion of carcinoma, the procedure should be, in effect, a lumpectomy, using wide local excision of the intact tumour surrounded by a cuff of tumour-free tissue (by palpation and visual inspection). The specimen should be orientated with sutures or clips (Margolese, 1987). Tumour-involved margins should be re-excised. A clear margin is defined as one with no malignant cells at the cut surface. Separate incisions should be used for removal of the primary tumour and for axillary dissection except where these happen to coincide anatomically. Radial incisions should not be used except when directly medial or lateral

to the nipple (Margolese, 1987). The tumour bed should be tagged with clips to indicate the site of the tumour to the radiotherapist when a radiotherapy boost is used (Hunter, 1996; Krawczy,k 1996; Fein,1996 ; Machray, 1994)

3.2.2 Treatment of the Axilla

The benefits of axillary dissection in prolonging survival are unclear. The NSABP-04 trial (Fisher, 1985) found no survival difference between women who had mastectomy with axillary clearance and women with mastectomy alone, while another study by Cabanes (1992) found a small but significant improvement in survival in women who had axillary surgery (92.6% vs 96.6% p=0.014) (Cabanes,1992). However both of these studies may be flawed, since 33% of the non-dissected group in the NSABP-04 study had some form of limited dissection, while significant proportion of the axillary dissection group in the Cabanes study received adjuvant systemic therapy based on their nodal status (Level III). The definitions of the various forms of axillary dissection are indicated in Appendix 4. Patients should be made fully aware of the frequency and severity of the potential complications of axillary dissection (Recht, 1995). Wherever possible, the intercostobrachial nerve should be preserved, unless preservation compromises disease removal, as it reduces post-operative numbness (Abdullah, 1998)(Level II-1).

Limb physiotherapy is advised immediately after axillary dissection (Recht, 1995). Omission of axillary dissection may be considered when the risk of axillary metastases is very low or when knowledge of node status will have no influence on therapy. However such subgroups have not been clearly defined (Recht, 1995; Whitworth, 2000)(Level III).

Axillary node biopsy may fail to detect metastases in 42% of patients and axillary node sampling may miss 14% of patients with axillary metastases (Davies, 1982). Hence, a significant number of involved nodes would not be detected by some forms of axillary sampling (Davies, 1982; Graverson, 1988; Veronesi, 1987)(Level II-3). Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early invasive breast cancer (Recht, 1995; Whitworth 2000). For accurate staging, at least level I and II nodes should be removed (Recht, 1995) (Level II-1). A full clearance of up to Level III should be carried out in the presence of clinically involved nodes (Recht, 1995). In an adequate clearance, the number of nodes retrieved should be at least 10 (Level III).

Sentinel lymph node biopsy (SLNB) is appropriate if an experienced sentinel lymph node team is available with facilities for both the dye and albumin radiocolloid technique (Whitworth, 2000). Candidates for sentinel node biopsy should have clinically negative axillary lymph nodes, solitary T1 or small T2 primary, no large haematoma or seroma in the breast, and no prior neoadjuvant chemotherapy. The SLN can be identified in over 97% of patients if both the dye and radiocolloid technique are used together, with a false negative rate of 5% (Veronesi, 1997; McIntosh, 1998; Ragaz, 1997; Krag, 1998) (Level II-1).

3.3 Management of Ductal Carcinoma-in-situ

Mastectomy as a primary outcome treatment is associated with a near-total avoidance of recurrence after 3-20 years. Lumpectomy alone is associated with a high recurrence rate of 20%. Breast conserving surgery (BCS) followed by radiotherapy is associated with a local relapse rate of 6-12% after 8 years (Bijker, 2001; White, 1995; Fisher, 1993) (Level I) (see Appendix 5 for a review of the evidence). Existing data show no difference in survival between BCS or mastectomy. Size, margin status, grade and comedo-type necrosis are predictors of local recurrence (Fonseca, 1997; Wright & Van Zee, 1999; Bradley, 1990; Bijker, 2001; White, 1995; Fisher, 1993; Viccini, 2002) (Level I). Younger patients have also shown a significantly higher rate of local recurrence after BCS and radiotherapy than older patients (Bijker, 2001; White, 1995; Fisher, 1993; Viccini, 2002) (Level II-3).

There is some evidence that patients with low-grade lesions with clear margins greater than 1 cm may be able to forgo breast irradiation since they have a relatively low risk of recurrence (Fonseca 1997; Wright & Van Zee 1999) (Level III).

Mastectomy is indicated when lesions are so large or diffuse that they cannot be completely removed without causing unacceptable cosmesis or when there is persistent marginal involvement, especially with high-grade malignant lesions. Subcutaneous mastectomy should not be used to treat DCIS (Fonseca, 1997; Wright & Van Zee, 1999; Bradley, 1990; Bijker, 2001; White, 1995; Fisher, 1993). Axillary surgery, whether as a full or limited procedure, should not usually be performed in women with DCIS (Fonseca, 1997; Wright & Van Zee, 1999).

The other contraindications for BCS in ductal carcinoma-in-situ are similar to BCS for invasive cancers.

A randomised, blinded, placebo-controlled trial (NSABP-24) demonstrated that adding tamoxifen to lumpectomy and radiation therapy was effective in preventing cancer in the ipsilateral and contralateral breast at 5 years without affecting survival (Fisher, 1999) (Level I). Further analysis suggests that tamoxifen may be effective only in DCIS which are ER positive (Allred et al, 2002)

3.3 Management of Lobular Carcinoma-in-situ

LCIS is a marker of increased risk for the development of breast cancer, and does not require treatment. The risk of breast cancer is equal in both breasts, estimated at 21% over 15 years (NCCN Practice Guidelines in Oncology, 2002; Haagensen, 1981). Close surveillance with clinical examination and annual mammography is indicated (NCCN Practice Guidelines in Oncology, 2002). If the patient wishes to minimize risk absolutely, bilateral mastectomy with or without breast reconstruction has been advocated (Wright & Van Zee, 1999; Haagensen, 1981)(Level III).

3.4   Management of Locally Advanced Breast Cancer
Multimodality treatment using a combination of surgery, chemotherapy, radiotherapy and hormonal therapy is the choice of treatment for locally advanced breast cancers. (Stage III a and IIIb) (NCCN Practice Guidelines in Oncology, 2002; Wilsher & Hortobagyi, 1999) (Level II-2).

In Stage III operable cancer, the choice is between mastectomy and axillary dissection or neoadjuvant chemotherapy followed by surgery. No survival difference has been noted between the two treatment options. In Stage IIIa and IIIb inoperable cancer, the treatment of choice is neoadjuvant chemotherapy followed by surgery for those who respond to chemotherapy.   Those who remain inoperable after chemotherapy should be given radiotherapy (NCCN Practice Guidelines in Oncology, 2002)(Level III).

In patients with progressive disease despite neoadjuvant chemotherapy, treatment should be individualized depending on the patient's circumstances.

3.5   Breast Reconstruction
Immediate breast reconstruction can be performed following mastectomy for cancer without increased risk for overall post-operative complications, local or distant recurrence (O Brien et al, 1993)(Level II-3).

Who should be offered breast reconstruction?
*   Patients who are less than 55 years old
*   DCIS, LCIS and Stages I and II breast cancer
*   Patients who are undergoing prophylactic mastectomy
Caution: Patients who are diabetic, obese, and who smoke should be warned of the risk of increased complications should they opt for breast reconstruction (Beckenstein, 2001).

The full range of reconstructive options (from creation of the breast mound to nipple-areolar reconstruction), the resultant scars, the possible complications and the advantages and disadvantages of each individual strategy should be explained to the patient. The aim of the surgeon is to sensitively guide the patient in her own decision-making process by providing comprehensive and necessary information without any form of pressure or coercion (Beckenstein, 2001; Wilkins, 2000).
The choice of immediate or delayed reconstruction should be discussed within the team and with the patient, the logistics of the local situation being the major factor in deciding which is more appropriate. If it is judged that the patient is likely to require post-operative radiotherapy, delayed reconstruction should be considered. Should the patient still opt for immediate reconstruction, she should be informed of the effects of radiotherapy on the reconstructive result (Tran, 2001) (Level II-3).
3.6   Management of Metastatic Breast Cancer
The aim of treatment of metastatic breast cancer is to palliate symptoms and to maintain the best possible quality of life (Elli,s 1999) (Level III). The recommendation for Stage IV cancer with an enlarged supraclavicular lymph node as the only metastatic lesion, is to treat as Stage IIIb (NCCN Practice Guidelines in Oncology, 2002)(Level III). The

metastases should preferable be proven by biopsy, in patients with a suspected solitary metastatic lesion (Ellis, 1999).

In metastatic breast cancer the choice of chemotherapy, hormone therapy and immunomodulation (such as Herceptin) should be individualized depending on the patient's physical condition and financial constraints (NCCN Practice Guidelines in Oncology 2002) (Level III). A variety of new cytotoxic agents (such as Paclitaxel, Docetaxel, Vinorelbine, Gemcitabine, Caelyx or liposomal Doxorubicin, Capecitabine), hormonal agents (Anastrazole Letrozole, Exemestane) and immunomodulators (Trastuzumab) are entering use in the management of advanced breast cancer. Through the use of new delivery vehicles such as liposome encapsulation or through different treatment schedules, such as oral 5-FU analogs or weekly taxanes, the tolerability of traditional drugs have been enhanced. Phase 2 studies have shown varying response rates with these new agents; however a survival benefit has not been clearly demonstrated. Patients with metastatic breast cancer should have their treatment determined by tumour expression of such biological markers as estrogen/progesterone receptors and the c-cerbB-2 oncogene (Burstein, 2001).

For premenopausal patients with advanced breast cancer which is ER positive, ovarian ablation for inducing menopause is recommended (Kljn, 2001) (Level II-1).

In a patient with Stage IV breast cancer with a fungating breast mass, who is fit and agreeable to surgery, a toilet mastectomy is indicated. If primary skin cover is not possible, skin cover may be achieved with any form of a full-thickness skin flap (Ellis, 1999).

3.8   Adjuvant Radiotherapy

Adjuvant radiotherapy is indicated after breast conserving surgery (BSC) for early invasive breast cancer. Omission of radiotherapy after BCS almost always increases the risk of local recurrence. While recurrences may be salvaged by mastectomy, the rate is more than 20% at 5 years (Fisher,1989; Fisher, 1995) (Level I).

Post mastectomy chest wall adjuvant radiotherapy is indicated when the risk of local recurrence is high, i.e. when the tumour is T3 and above, lymph node metastases is present especially with equal to or more than 4 nodes positive, where margins are involved or less than 5 mm (Overgaad, 1997; Ragaz, 1997; Overgaad, 1999; Diab, 1998) (Level III). Randomized controlled trials show a survival benefit of 5% at 15 years with post mastectomy chest wall irradiation (Overgaad, 1997; Ragaz, 1997; Overgaad, 1999) (Level I). Due to improved radiotherapy techniques in post mastectomy radiotherapy, there has been no significant increase in non-breast cancer deaths,(mainly vascular in origin), that has been demonstrated in later trials (Valgussa, 1995; Gyenes, 1994; Fuller, 1992; Augquier, 1992; Diab, 1998; Paszat, 1998; Nixon, 1998; Cuzicks, 1994; Recht, 2001; EBCTG, 2000; Whelan, 2000). Breast radiotherapy should also be suggested to patients who have undergone a wide local excision for ductal carcinoma in situ (Fisher, 1996) (Level I).

It is recommended that local breast/chest wall irradiation should be given as soon as possible after surgery and not later than 12 weeks after, except in whom radiotherapy is preceded by chemotherapy. However the optimal sequencing of chemotherapy and irradiation is not clearly defined for patients who are also candidates for chemotherapy. Most centers favour the administration of chemotherapy before radiotherapy. Selected chemotherapy regimens are sometimes used concurrently with radiotherapy. Concurrent chemo-radiotherapy has not been shown to be associated with better outcome and there is a possible risk of increased reaction and poorer cosmesis. Doxorubicin should not be given concurrently with radiation (Meek, 1996; Vujovic, 1998; Hartsell, 1995)(Level III).

The use of radiation boost to the primary tumour bed is recommended as it reduces the risk of recurrence (Bartelink, 2001) (Level II-3). However, the boost therapy is not recommended for DCIS.

Breast cancer is a moderately radiosensitive tumour. With appropriate tumour dose at par with the tumour volume, radiation can result in significant tumour control rates. The microscopic disease in a post mastectomy chest wall requires about 50Gy (or bioequivalent) to control up to 90 % of the disease in the tumour bed; whereas a gross tumour of 2 cm diameter requires a dose of at least 60 Gy (or bioequivalent) for a similar control rate (Van Limbergen, 1990).

In patients in whom surgery is contraindicated, higher doses of radiation are required. A minimum does of 60Gy (or bioequivalent) would be required for a T1 tumour and a bigger tumour would require more than 70Gy (or bioequivalent). However, an alternative form of anaesthesia and surgery should be considered before utilizing primary radiotherapy for breast cancer (Van Limbergan, 1990).

Is there a role for axillary radiotherapy?
Axillary radiotherapy is indicated in invasive cancers where axillary dissection was not done, where there is obvious disease post-dissection, and for node positive patients where dissection is inadequate (less than 4 nodes found) (Recht 1995). Axillary irradiation for extra-capsular extension remains controversial (Donegan, 1993; Fisher, 1997) (Level III).

The role of supraclavicular radiotherapy post-axillary dissection is controversial. No randomized study has been done to address this issue. Retrospective analysis suggest high rates of recurrences for patients with more than 4 positive nodes, but there is no data on the impact of SCF irradiation on survival (Diab, 1998)(Level II-3).

The internal mammary nodes are not irradiated routinely. Radiation may be considered for patients with T3 tumours, node positive patients especially more than 4 nodes positive (Marks, 1994) (Level III).

3.9   Adjuvant Chemotherapy
Breast cancer is a moderately chemo-sensitive tumour. High response rates can be seen in untreated tumours in the neo-adjuvant and metastatic settings. In the adjuvant setting, modest gains in relapse-free survival and overall survival can be obtained with a short

course of chemotherapy (EBCTG, 1998; EBCTG, 2001, Hortobagyi, 1998; Fisher, 1997; French Adjuvant Study Group, 2001; Levine, 1998)(Level I) (See Appendix 6 for estimates of proportionate risk reduction from polychemotherapy).

Adjuvant chemotherapy should be offered to all patients in the high-risk category:

- All node positive patients
- Patients with tumours 2 cm or more
- Patients with ER negative tumours

It may be considered in the following patients in the moderate risk category:

- All patients with tumours 1-2 cm
- Patients with high grade (Grade 3) tumours
- Patients with tumours with lymphovascular invasion

Adjuvant chemotherapy is not required in patients in the low-risk category, that include

- All patients with tumours less than 1 cm
- Patients with tumours of special types of histology (tubular, mucinous and cribriform) less than 2 cm.

(NCCN Practice Guidelines in Oncology, 2002; St Gallen- Guideline for adjuvant therapy for breast cancer, 2001)(Level III)

Adjuvant chemotherapy should be started 4-6 weeks after surgery, since there is no benefit in administering delayed chemotherapy (Wallgren, 1996; Recht, 1996; Markiewicz, 1996)(Level III).

What are the current chemotherapy regimens being used?

Acceptable adjuvant chemotherapy regimes are:

- CMF for 6 cycles (Cyclophosphamide, Methotrexate and 5-Fluorouracil)
- AC for 4 cycles (Adriamycin and Cyclophosphamide)
- FAC or FEC for 4-6 cycles (5-Fluorouracil, Adriamycin or Epirubicin and Cyclophosphamide)

(French Adjuvant Study Group, 2001; Levine, 1998; NCCN Practice Guidelines in Oncology, 2002; St Gallen- Guideline for adjuvant therapy for breast cancer, 2001) (Level I)

The role of Taxanes in the adjuvant setting is still investigational (NCCN Practice Guidelines in Oncology, 2002).

3.10   Adjuvant Hormone Therapy
Should Tamoxifen be given to all breast cancer patients?

Adjuvant Tamoxifen 20 mg daily for 5 years should be offered to all patients with ER positive tumours and in patients where ER status is unknown as it has been shown to improve recurrence free survival and overall survival (EBCTG, 1998)(Level I). It may also be considered in post-menopausal patients with ER negative tumours. The effects of use of Tamoxifen in ER negative but PR positive patients are not known, while its use in ER negative, pre-menopausal patients is not recommended (EBCTG, 1998; Pritchard, 2001; Fisher, 2001)

There is a small risk of endometrial carcinoma associated with the long-term use of Tamoxifen for more than 5 years (Bergman, 2000) (Level II-3).

Other adjuvant therapy

The role of Aromatase inhibitors in postmenopausal patients in the adjuvant setting is still in the investigational stage, while its use in pre-menopausal patients is contra-indicated. (St Gallen- Guideline for adjuvant therapy for breast cancer, 2001).

Hormonal therapy should not be used concurrently with chemotherapy (Pritchard, 2001)(Level III).

3.11   Bisphosphonates In Breast Cancer

Bisphosphonates is not recommended as adjuvant therapy currently, since there is conflicting data on its use - decreased metastases and improved survival in two trials (Diel, 1998; Powles, 2002), decreased survival in another trial (Saarto, 2001) and no difference in two other trials (Mardiak, 2000; Powles, 1998) (Level 1). Intravenous bisphosphonates may be used as an adjunct with chemotherapy or hormone therapy in women with pain due to skeletal metastases (Hillner, 2000).

While Bisphosphonates reduce the incidence of skeletal complications in bone metastases in those women with documented lytic destructive lesions, its role in women with abnormal scans without bone destruction is unproven (Kristensen, 1999; Hortobagyi, 1996; Lipton, 2000; Theriault, 1999)(Level I). The use of Bisphosphonates for the prevention of skeletal events is associated with significant increase in medical costs (Hillner, 2000).

3.12   Follow-Up
All patients with breast cancer should be followed up, since most recurrences occur in the interval of follow-up. After completion of treatment of breast cancer, follow-up should be coordinated and not duplicated. (Temple, 1999).

The objectives of follow-up are to:
- provide patients with support and counselling
- detect potentially curable conditions such as local recurrence of cancer in the breast following BCS, and to detect new cancers in the opposite breast
- manage patients in whom metastatic disease develops, and to determine outcome(NHMRC)

The suggested follow-up schedule is as follows:
- 3 monthly for the first 2 years
- 6-monthly for the next 3 years
- Yearly thereafter

During follow-up, history and physical examination should be carried out. Blood tests and diagnostic imaging have not been found to improve survival or quality of life more than does physical examination for detecting distant metastases. The patient is also advised to carry out monthly breast self-examination (Robertson, 1988; Temple, 1999; The GIVIO Investigators, 1994; Grunfeld, 1996; Del Turco, 1994) (Level I).

While there is no data to show that mammography improves survival when used for detection of local recurrence or contra-lateral breast cancer, it has been suggested that annual mammography after therapy for primary breast cancer makes good sense (Robertson, 1988; Temple, 1999; The GIVIO Investigators, 1994; Grunfeld, 1996, Del Turco, 1994) (Level I). After breast conservation surgery, the first mammogram of the affected breast should be performed 6 months after completion of radiotherapy (NCCN Practice Guidelines in Oncology, 2002).

3.13   Management of Bone Metastases in Breast Cancer
In the absence of any other disease, a solitary lesion on bone scan should be confirmed by bone biopsy for unequivocal evidence of the diagnosis of metastases. For confirmed bone metastases (solitary or multiple), full staging investigations (imaging of the lungs and liver) should be carried out before treatment (NHMRC). Referral to an orthopaedic surgeon with special interest in bone metastases should be made early (BASO Guidelines for the Management of Metastatic Bone Disease in Breast Cancer in the United Kingdom, 1997).

It is suggested that any lesion in weight-bearing bone should be imaged to determine the risk of fracture, since there is a high risk of fracture once 50% of the cortex is lost. Prophylactic fixation of the bone should be carried out. Similarly, fixation or stabilization should be carried out following pathological fracture (Fidler, 1981). For metastatic disease of the spine, patients who may benefit from surgical stabilization are those with pain, with over 50% of vertebral body destruction and/or pedicle destruction without collapse, or those with moderate deformity and collapse (NHMRC, 2001).

Patients with spinal cord compression need urgent MRI or CT myelogram as well as urgent assessment by the orthopaedic or neurosurgeon and oncologist. Where immediate surgery is not possible, it is recommended that the patient be started on high-dose steroids

(16 mg Dexamethasone daily). There is insufficient data to demonstrate that surgical decompression and stabilization followed by radiotherapy, offers an improved quality of life compared to providing only radiotherapy. However, there should not be delay in providing radiotherapy if surgery is not carried out (Siegal, 1989; Posner, 1987; Arcangeli, 1998; Jeremic, 1998; Loblaw, 1998; Sorenson, 1994)(Level II-2).

3.14 Management of Malignant Hypercalcaemia

Hypercalcaemia (corrected calcium > 2.6 mmol/l) can occur in the presence of bone metastases. It may also be due to the production of a parathyroid hormone-like substance by the tumour. A diagnosis of hypercalcaemia may be considered in a breast cancer patient who develops thirst, polyuria, nausea and vomiting, hypotension or mental confusion. However, it can also be asymptomatic (NHMRC). In those asymptomatic patients with normal renal function, a single infusion of a Bisphosphonate should be administered (Purohit, 1995).

If the patient is unwell, has very high serum calcium (>3.5mmol/l), or has impaired renal function, she should be provided emergency inpatient treatment as follows:
- Hydration with normal saline infusion, to ensure good diuresis
- Bisphosphonate infusion (Level II-1)
- Correction of hypokalemia (if present) with 20 mmol KCl in each pint of normal saline
- Continued hydration until the patient is able to maintain high oral fluid intake (NHMRC, 2001; Purohit, 1995).

3.15 Palliative Care

The primary indication for referral to the palliative care team should be those patients with advanced and progressive disease with significant physical, psychosocial and spiritual needs. The secondary indication for referral to the palliative care team, however, is any patient with the above problems, which may be arrested by palliative intervention, regardless of stage of the disease.

Palliative care should not be seen as preparation for death, but rather to maximize the quality of life, in the time remaining for the patient with advanced disease. Palliative care may be especially helpful in maximizing the patient's performance status in the home environment. Palliative care has been shown to improve patient outcome in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction, and control of pain, symptoms and family anxiety (Hearn 1998)(Level I).

4.   MANAGEMENT OF BREAST CANCER IN SPECIFIC GROUPS

4.1   Breast Cancer in Pregnancy

For pregnant patients with Stage 1 or 2 and some of those with Stage 3 breast cancers, modified radical mastectomy without delay is the best option (Di Fronzo, 1996; Petrek, 1994; Berry, 1999) (Level III). Breast conservation surgery is contraindicated because irradiation may cause permanent conditions regardless of the trimester of pregnancy. However, breast conservation can be carried out in late pregnancy, and irradiation given after delivery (Di Fronzo, 1996; Petrek, 1994; Berry, 1999).

Although termination of pregnancy allows full treatment to the mother, it does not alter the prognosis.   However, in early pregnancy, termination of pregnancy may be considered if maternal treatment options such as chemotherapy or radiotherapy are significantly limited by the continuation of the pregnancy (Di Fronzo, 1996; Petrek, 1994; Berry, 1999).
Chemotherapy can be given after 16 weeks' gestation, but this may increase the risk of premature birth, fetal growth restriction, maternal and fetal myelosuppression, and stillbirths (Kimberly, 2002; Buekers, 1998) (Level III).

4.2   Male Breast Cancer

Male breast cancer is very rare, occurring in only 1% of breast cancers. Prognostic factors and stage-for-stage outcomes are similar to those for the disease in females. The treatment is similar to breast cancer in females (Vetto, 1999; Williams, 1996)(Level III).

4.3   Breast Cancer in the Elderly

Breast cancer in the elderly is often defined as breast cancer developing after the age of 70 years old.   Treatment must take into account the functional status and quality of life (Lickley, 1997). Elderly patients with breast cancer are often under-treated by conventional criteria, although the rates of local recurrence and distant metastases are not significantly increased in comparison with conventionally treated elderly patients. Standard therapys such as axillary dissection, radiotherapy and chemotherapy, have a considerable morbidity in the elderly, and may not be well-tolerated (Gajdos, 2001).

The optimum treatment for elderly patients with operable breast cancer is surgery followed by Tamoxifen, while frail elderly patients should be treated with Tamoxifen alone.   Several randomized controlled studies have shown that although there was no difference in survival between surgery combined with Tamoxifen and Tamoxifen alone, failure of locoregional control was significantly higher in the Tamoxifen group.   The type of surgery ranges from simple excision without axillary dissection if clinically node negative to mastectomy with axillary dissection (Riley, 1994; Robertson, 1992; Bates, 1991; Robertson, 1988) (Level I).

4.4   Pregnancy after Breast Cancer

Pregnancy in women who have had low-risk breast cancer is relatively safe after 2 years. Tamoxifen should be stopped prior to conception. However, it is prudent to advise avoiding pregnancy in women at high risk for recurrences (Kroman, 1997) (Level III).

4.5   Hormone Replacement Therapy after Breast Cancer

Many breast cancer patients are menopausal at the time of diagnosis, or rendered menopausal from adjuvant chemotherapy, and may experience bothersome menopausal symptoms such as hot flushes, and mood and sleep disturbances. Data on the effect of Hormone Replacement Therapy (HRT) among breast cancer survivors are limited to non-randomized studies, mostly case series where HRT was started after a mean disease-free survival of 52 months. While it can be concluded that HRT use by women with a history of invasive breast cancer does not significantly increase the risk of breast cancer recurrences, it needs to be emphasized that these findings are based on observational data subject to a variety of biases (Col, 2001)(Level III).

5.   SCREENING FOR BREAST CANCER

The aim of screening by mammography is to detect breast cancer at an early stage or before it is physically evident, so that patients are cured more easily, possibly at less expense. Trials on population-based screening mammography have demonstrated an approximately 30% reduction in mortality from breast cancer in the screened population after 8 years, most marked in women aged 50-70 years (Nystrom Lrutqvist, 1993; Roberts, 1990; Shapiro, 1988; Andersson, 1988; Frisell, 1991; Heimann, 1998; Rosenquist, 1998)(Level I) (See Appendix 8 for list of studies on screening). However, population-based screening in Malaysia is not recommended, due to limited resources as well as the lack of local statistics on mammography and breast cancer.

Screening, however, may be considered in high risk women (with a past history of breast and/or ovarian cancer, family history of breast cancer in one or more first or second degree relatives before the age of 50 years, and a history of atypia on previous breast biopsy) below the age of 40 years, at the discretion of doctor and the wish of the patient. The value of mammographic screening should be explained to those asymptomatic women, aged 40-49 years, who have expressed their wish to be screened; however, they should not be discouraged from seeking such services (Shapiro, 1988; Anderson, 1988; Frisell, 1991; Tabar, 1999). In these situations, mammography should be done annually in women aged 40-49 years, and annually or biennially in those 50-75 years old (Diagnosis of Breast Diseases, 2001; Tabar, 1999) (Level 1) (See Appendix 8 for details of the mammogram report).

In patients on postmenopausal hormone replacement therapy (HRT), a screening mammogram should be performed before therapy is started to establish a baseline, as well as to ascertain the absence of any malignancy or other lesions. Although the frequency of screening can be at the discretion of the doctor and the patient, it would be prudent to perform annual or biennial screening if the patient has been on HRT for more than 5 years (Collaborative Group on Hormonal Factors in breast cancer, 1997; Chen 2002) (Level III).

High resolution ultrasound is the first diagnostic imaging method in women less than 35 years for symptomatic women; however, this is not recommended for screening. In

screening mammography, ultrasound is a useful adjunct and is recommended in the assessment of a patient with dense parenchymal pattern on mammograms. It is most useful in differentiating cysts from solid masses, thereby avoiding unnecessary biopsies (Basset, 1991).

5.1 Evaluation of a Non-Palpable Mammographic Abnormality

Once an abnormality is detected on the mammogram, additional mammographic studies (compression, spot and magnification views) and / or ultrasound should be done if needed to complete characterisation of the lesion. Should this not be possible at the time of the patient's examination, the report should reflect the inadequate or incomplete assessment. The patient should be recalled where deemed necessary and communication with the referring physician established. The current mammogram should be compared to previous studies wherever possible. It is left to the discretion of the radiologist as to how vigorously to pursue previous mammograms (The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998).

In image-guided biopsy or pre-biopsy localization procedures, a full report should be made as for surgical notes for a surgical procedure. In pre-biopsy localization or in core biopsy especially for calcifications or a mass, specimen mammography can be helpful to confirm the presence of the mammographic abnormality. The radiologist should submit a report to confirm removal of the abnormality or otherwise (The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 1998).

6. COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine therapies appear to be widely used by breast cancer patients in many parts of the world. A systematic review of relevant published data located 26 surveys of cancer patients conducted in 13 countries. It indicated that nearly one-third of cancer patients used complementary and alternative therapies (Ernst, 1998).

Complementary therapies, such as massage and relaxation methods, are used adjunctively along with mainstream care for symptom management and to enhance quality of life. Alternative therapies are active biologically, often invasive, and typically promoted as cancer treatment to be used instead of mainstream therapy. Complementary therapies can be helpful, but alternative medicine, because it can create direct physiologic interference or indirect harm by keeping patients from receiving timely care, presents serious problems to both the oncologist and the patient (NHMRC, 2001).

Alternative therapies are divided into:
- Diets and supplements (e.g. Gerson diet)
- Botanicals (e.g. Mistletoe,Reishi mushroom)
- Unconventional agents (e.g. shark cartilage, ozone, chelation)
-

- Traditional medicine (e.g. acupuncture, folk medicine)
- Energy healing and others (e.g. magnetic fields, detoxification, urine therapy)

(Alternative Medicine Use Worldwide, 2001)

Although most alternative therapies are of unproven value, attempts to dissuade patients from using them will be ineffective. Such attempts may result in people using alternative therapies not talking to their doctors about them. It is essential that, for reasons of safety, doctors are aware of any alternative therapies that their patients may be using, and should offer to discuss any alternative therapy the patient or her family wishes to talk about. (Ernst 1998; Alternative Medicine use Worldwide, 2001)(Level III).

## 7.	PREVENTION OF BREAST CANCER

Breast cancer cannot be prevented; however the risk of breast cancer may be reduced by avoiding the "affluent diet" and the promotion of a healthy diet and lifestyle. The following key principles should be observed:
- Avoid excessive fat
- Adequate amounts of vegetables, fruits and whole grains with fibre in the diet
- Adequate exercise and a moderate calorie intake
- Prevent contamination of food by carcinogens such as aflatoxin and chemicals used such as pesticides, and avoid adding to food substances such as nitrites and nitrates

(Manual On the Prevention and Control of Common Cancers 1998)

Secondary prevention is by screening through breast self-examination (BSE), health worker breast examination (HWBE) and mammography. BSE offers the most practical method of early detection, and several studies have demonstrated that an effective BSE education programme leads to a shift to an earlier stage of breast cancer diagnosis (Hill 1988) (Level II-1). It is suggested that health workers examine the breasts whenever a woman attends the clinic, and at the same time, BSE should be taught and the correct procedure reinforced.

In women who are carriers of the BRCA1 and BRCA2 mutations, the risk of developing breast cancer has been estimated to be more than 80% by the time they reach 65 years old. A retrospective study in women with BRCA1 and BRCA2 mutations, but with no history of breast cancer, shows a significant reduction in the risk of breast cancer with prophylactic bilateral oophorectomy (Rebbeck, 2002) (Level II-3).

8. ALGORITHM FOR INVASIVE BREAST CANCER STAGE I, IIA AND IIB

Clinical Stage	Investigations	Primary treatment	Pathology	Adjuvant therapy
Stage I Stage IIa Stage IIb (See Appendix 1 for staging)	FBC, LFT CXR Mammogram	* Lumpectomy + Axillary dissection + Radiotherapy	Node negative	[1]Low risk - no chemotherapy [2]Moderate risk – consider chemotherapy [3]High risk – chemotherapy
		Mastectomy + Axillary dissection +/- reconstruction	Node positive	Chemotherapy Chest wall radiotherapy especially if more than 4 lymph nodes involved Consider radiotherapy to supraclavicular region if more than 4 nodes involved
*Contraindications Multifocal disease Pregnancy Large tumour Patient's preference for mastectomy Inavailability of radiotherapy facilities			ER positive	Tamoxifen (after chemotherapy where required)
			ER negative	Consider tamoxifen in postmenopausal women No tamoxifen in premenopausal women
[1] Low risk Less than 1 cm Special histology types(tubular, mucinous and cribriform) with tumours less than 2 cm			Tumour > 5 cm or margins involved	Chest wall radiotherapy
[2] Moderate risk 1-2 cm High-grade Lymphovascular invasion				
[3] High risk More than 2 cm ER negative				Acceptable adjuvant chemotherapy regimes CMF 6 cycles AC 4 cycles FAC/FEC 6 cycles

9. ALGORITHM FOR INVASIVE BREAST CANCER STAGE III and IV

Clinical Stage	Investigations	Primary treatment	Adjuvant treatment

Operabl

Mastectomy and axillary dissection
or
Neoadjuvant chemotherapy followed by mastectomy and axillary dissection

Chemotherapy followe
by radiotherapy to ches
wall Tamoxifen if EI
positive

Stage IIIa
Stage IIIb

FBC
LFT
CXR, Mammogram
US liver / CT liver/lungs
Bone scan
Biopsy with ER

Inoperab

Neoadjuvant chemotherapy:

-If there is response mastectomy and axillary clearance

- If no response individualised therapy

Additional chemotherapy an
radiotherapy to ches
wall Tamoxifen if EI
positive

Stage IV

FBC, LFT
CXR, Mammogram
US liver/ CT liver/ lungs
Bone scan biopsy with ER

Treatment is indivualised depending on physica
condition, ER status, cerbB2 status, utilizing variou
options of surgery, chemotherapy, hormonal therapy
immunotherapy and radiotherapy to optimize quality o
life and to palliate symptoms

10. ALGORITHM FOR INVASIVE BREAST CANCER STAGE 0

Diagnosis	Investigations	Primary treatment	Àdjuvant treatment

Ductal carcinoma in situ Stage 0

Mammogram

Widespread

Mastectomy without lymph node dissection+/- reconstruction → Consider Tamoxifen for 5 years

Localised → Lumpectomy and *Radiotherapy or Mastectomy without Lymph node dissection

+/- reconstruction → Consider Tamoxifen for years

*Low grade lesions, small lesions with clear margins may not require radiotherapy after wide excision

Lobular carcinoma in situ Stage 0

Mammogram

Increased surveillance or bilateral mastectomy+/- reconstruction

Tamoxifen can be considered for prevention

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<div align="center">AJCC STAGING (TNM CLASSIFICATION) (6TH EDITION)</div>

Primary Tumour (T)

TX: Primary tumour cannot be assessed

T0:   No evidence of primary tumour

Tis: Carcinoma in situ

Tis (DCIS) – Ductal carcinoma in situ

Tis (LCIS) – Lobular carcinoma in situ

Tis (Paget's) – Paget's disease of the nipple with no tumour

Note: Paget's disease associated with a tumour is classified according to the size of the tumour

T1:   Tumour 2.0 cm or less in greatest dimension
        T1mic: Microinvasion 0.1 cm or less in greatest dimension
        T1a: Tumour more than 0.1 cm but not more than 0.5 cm in greatest dimension
        T1b: Tumour more than 0.5 cm but not more than 1.0 cm in greatest dimension
        T1c: Tumour more than 1.0 cm but not more than 2.0 cm in greatest dimension

T2:   Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension

T3:   Tumour more than 5.0 cm in greatest dimension

T4:   Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below. Chest wall includes ribs, intercostals muscles, and serratus anterior muscles but not pectoral muscle.
        T4a: Extension to the chest wall
        T4b: Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
        T4c: Both of the above (T4a and T4b)
        T4d: Inflammatory carcinoma*

*Note: Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. The clinical presentation is due tumour embolization of dermal lymphatics with engorgement of superficial capillaries.

Regional lymph nodes

NX: Regional lymph nodes cannot be assessed (e.g. previously removed)

N0:   No regional lymph node metastases

N1:   Metastases to movable ipsilateral lymph nodes

N2: Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary lymph nodes in the absence of clinically evident axillary lymph node metastasis

N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures.

N2b: Metastasis only in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph nodes.

N3: Metastases to ipsilateral infraclavicular lymph node(s), with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement.

N3a – Metastasis in ipsilateral infraclavicular lymph node(s)

N3b – Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c – Metastasis in ipsilateral supraclavicular lymph node(s)

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Pathologic Classification (pN)[1]

PNX: Regional lymph nodes cannot be assessed (not removed for pathological study or previously removed)

PN0: No regional lymph node metastases histologically, no additional examination for isolated tumour cells (ITC)

Note: Isolated tumour cells (ITC) are defined as single tumour cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods, but which may be verified on H&E stains. ITC's do not usually show evidence of malignant activity (eg proliferation or stromal reaction).

1. Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designates (sn) for "sentinel node"(eg pN0(i+)(sn))

PN0(i!) – no regional lymph node metastasis histologically, negative IHC

PN0(i+) – No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm.

PN0(mol!) – No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[2]

PNO(mol+) – No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[2]

2. RT-PCR – reverse transcriptase / polymerase chain reaction

PN1: Metastasis in 1 to 3 axillary lymph nodes, and/or internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent*

> PN1mi – Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
> PN1a – Metastasis in 1 to 3 axillary lymph nodes
> PN1b – Metastasis in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*
>
> pN1bi, pN1bii, pN1biii, pN1biv excluded
>
> pN1c – Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes, with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent* (if associated with more than 3 positive lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumour burden)

PN2: Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent** internal mammary lymph nodes in the absence of axillary lymph node metastasis.

> PN2a – Metastasis in 4 to 9 axillary lymph nodes (at least 1 tumour deposit more than 2.0 mm)
> PN2b – Metastasis in clinically apparent** internal mammary lymph nodes in the absence of axillary lymph node metastasis.

*Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination
**Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical evaluation.

PN3: Metastasis in 10 or more axillary lymph nodes, or infraclavicular lymph nodes, or in clinically apparent) ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

> PN3a – Metastasis in 10 or more axillary lymph nodes (at least 1 tumour deposit greater than 2.0 mm) or metastasis to the infraclavicular lymph nodes.
>
> PN3b – Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent**

PN3c – Metastasis in ipsilateral supraclavicular lymph nodes.

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical evaluation.
**Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy)or by clinical examination

Distant metastases (M)
MX: Presence of distant metastasis cannot be assessed
M0:   No distant metastases
M1:   Distant metastasis

AJCC Stage groupings
Stage 0:   Tis, N0, M0
Stage 1:   T1, N0,M0

Stage IIA: T0,N1,M0
                T1, N1, M0
                T2,N0,M0
Stage IIB: T2, N1,M0
                T3, N0,M0
Stage IIIA: T0, N2, M0
                T1, N2, M0
                T2,N2,M0
                T3, N1, M0
                T3, N2, M0
Stage IIIB: T4, N0, M0
                T4, N1, Mo
                T4, N2, M0
Stage IIIC   Any T, N3, M0
                Any T, N3, M0
Stage IV: Any T, Any N, M1

(Ref: Breast. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. Philadelphia, Pa: Lippincott-Raven Publishers, 6th Ed., Effective Jan 2003)

DEFINITIONS OF DESCRIPTIONS OF BREAST CANCER

- Invasive breast cancer – cancer showing infiltration into the interlobular stroma i.e. outside the terminal duct lobular unit

- Minimal breast cancer – less than 1 cm (minimal invasive cancer), all non-invasive carcinoma irrespective of size (associated with 5-year survival of more than 95%)

- Microinvasive carcinoma – carcinoma in which the dominant lesion is non-invasive, but in which there are one or more foci of infiltration, none of which measures more than 1 mm (2 high power fields) in maximum diameter. (Note: small invasive carcinomas without an in-situ component are classified as invasive)

- Extensive intraductal component (EIC) - when the intraductal component comprises 25% or more of the area encompassed by the infiltrating tumour, and is also present in the surrounding breast tissue (Important predictor of local recurrence after excision and radiotherapy)

(National Coordinating Group for Breast Screening Pathology 1995; Diagnostic Histopathology of the Breast 1987)

Surgery for Stage I & II breast cancer - Breast conserving surgery vs. mastectomy –
a review of the evidence

Trial and Reference	Type of study	No	FU	Overall survival			Disease-free survival			Local recurrence		
				LRT	L	Mx	LRT	L	Mx	LRT	L	Mx
Veronesi etal 1981	RCT	701	5 yrs	90% (n=352)	NA	90% (n=349)	84%	NA	83%	1/352	NA	3/349
Fisher etal (NSABP-B06) 1989	RCT	1843	8 yrs	83%N-68%N+	76%N-60%N+	79%N-60%N+	66%N-47%N+	61%N-42%N+	66%N-45%N+	10%	39%	8%
Blichert-Toft etal DBCG-82TM 1992	RCT	905	6 yrs	82%	NA	79%	70%	NA	66%	NA	NA	NA
Van Dongen etal EORTC 10801 1992	RCT	902	8 yrs	71%	NA	73%	NA	NA	NA	15%	NA	9%
Fisher etal; NSABP B-06 1995	RCT	1529	12 yrs	63%	58%	59%	50%	45%	49%	10%	35%	NA
Jacobsen etal 1995	RCT	247	10 yrs	77%	NA	75%	72%	NA	69%	17%	NA	9%
Voogd AC etal DBCG-82TM EORTC 10801 2001	RCT	1772	10 yrs	67%	NA	67%	66%	NA	68%	10%	NA	9%

Key:

FU   Follow-up
RCT   Randomized controlled trial
LRT   Lumpectomy plus radiotherapy
L   Lumpectomy alone
Mx   Modified radical mastectomy
N -   Node negative
N+   Node positive
NA   Not available

DEFINITIONS OF THE VARIOUS FORMS OF AXILLARY DISSECTION

Sampling: removal of nodes from the lower axilla

Level I dissection: enbloc dissection of Level I (from latissimus dorsi to lateral border of pectoralis minor) up to the level of the axillary vein.

Level I-II dissection: enbloc dissection of lower and middle portion of the axilla, facilitated by elevation of pectoralis minor, and mobilisation of the ipsilateral arm to relax the pectoralis   major, latissmus dorsi laterally to the medial border of pectoralis minor, medially up to the level of the axillary vein.

Full axillary dissection (Levels I-III): removal of the entire axillary contents from latissmus dorsi laterally to subclavius muscle (Halsted's lIgament) medially, up to the level of the axillary vein with preservation of, or excision, of the pectoralis minor (Recht A 1995).

Surgery for ductal carcinoma-in-situ – Lumpectomy alone (L) vs. Lumpectomy and
Radiotherapy (LRT) – a review of the evidence

Study and Reference	Type of Study	No of pts	FU	Local recurrence	
				L	LRT
Fisher et al NSABP B-17 1993	RCT	818	8 yrs	26%	12%
Van Zee et al 1999	Retrospective	157	6 yrs	20.7%	9.6%
White J et al 1995	Retrospective	52	8 yrs	NA	6%
Bijker etal EORTC 10853 2001	RCT	863	5.4 yrs	18% (>40 yrs) 45% (< 40 yrs)	12% (> 40 yrs) 23% (<40 yrs)

Key:

FU   Follow-up
RCT   Randomized controlled trial
LRT   Lumpectomy and radiotherapy
L   Lumpectomy alone

Proportionate risk reduction from polychemotherapy

Age (yr)	Recurrence (% +/- SD)	Mortality (% +/- SD)
All	23.5 +/- 2	15.3 +/- 2
<40	37 +/- 7	27 +/- 8
40-49	34 +/- 5	27+/- 5
50-59	22 +/- 4	14 +/- 4
60-69	18 +/- 4	8 +/- 4
< 50 ER positive	33 +/- 8	20 +/- 10
ER negative	40 +/- 7	35 +/- 9
50-69 ER positive	18 +/- 4	9 +/- 5
ER negative	30 +/- 5	17 +/- 6

Source: Polychemotherapy for early breast cancer: an overview of the randomized trials EBCTG (The Lancet 1998;352)

Studies on screening mammography

Study	Type of Study	Period of study	Age at entry	No of women		Follow-up (median)	% reduction in breast cancer mortality in screened group
				Study	Control		
Shapiro et al (HIP) 1988	RCT	1963-69	40-64	14849	14849	18 yrs	33%
Nystrom et al (Overview of Swedish trials) 1993	RCT	1977-85	40-74	Combined cohort of 282 777 women		5-13 yrs	Overall 24% (50-69yrs -29%) (40-49yrs-13%)
Andersson et al (Malmo) 1988	RCT	1977-85	45-69	3658	3769	8.8 yrs	4%
Roberts et al (Edinburgh) 1990	RCT	1979-88	45-64	5913	5810	7 yrs	17%
Frisell J et al (Stockholm) 1991	RCT	1981-85	40-64	14375	7103	7.4 yrs	29%

THE MAMMOGRAM REPORT

The mammogram report should reflect whether the finding is normal, benign or suspicious and also indicate the further evaluation that may be essential to reach a diagnosis (American College of Radiology (ACR) Breast Imaging Reporting and Data System 3RD Edition). The follow up interval should also be recommended if this is the alternative to biopsy. The report would suggest one of the following findings:

- Need for additional imaging evaluation (findings for which additional imaging evaluation is required - if the department does not practice immediate reading of the mammogram by the radiologist, more likely arise in a screening programme)
- Negative or normal mammogram
- Benign finding (the radiologist may wish to describe a finding such as an involuting fibroadenoma, cysts, lipomas or secretory benign calcifications, intramammary lymph nodes and breast implants - these findings do not need tissue diagnosis; a report could also state that there is no mammographic evidence of malignancy). The patient can return to routine follow-up.
- Probably benign finding (0.5% to 2 % of these lesions may eventually turn out to be malignant). Short term interval follow-up is suggested. Lesions found have a high probability of being benign, and may not be expected to change during follow-up, however, this fact needs to be established. Indeterminate clusters of calcifications are included in this category. However, a few low-grade or early cancers can look benign. To date, adjunct ultrasound has not been as effective in differentiating benign from malignant solid masses, although new or improved sonographic techniques are being tested. When tissue diagnosis is preferred to close follow-up, emphasis on needle biopsy techniques should be made.
- Suspicious abnormality (20-40% are found to be cancer). The abnormal findings should be adequately described, and the degree of suspicion should be implied. Biopsy should be considered. These may include lesions that do not have characteristic morphologies of breast cancer, but have definite probability of being malignant.
- Highly suggestive of malignancy (75-90% found to have cancer). Appropriate action should be taken. These lesions have a high probability of being cancer.

Communication between the radiologists, surgeons, primary care providers is important. The patient should at all times be informed of findings and decisions. Where follow-up is necessary and the patient is referred back to the primary care provider (should this not be the surgeon / breast clinic specialist) then the findings must be conveyed, and it is the responsibility of the primary care provider to supervise the follow-up.