CLINICAL PRACTICE GUIDELINES

2019

MOH/P/PAK/432.19(GU)-e

MANAGEMENT OF BREAST CANCER

(Third Edition)

Ministry of Health Malaysia

Academy of Medicine Malaysia

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia

ISBN: 978-967-2173-99-1

Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare 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.

UPDATING THE CPG

These guidelines were issued in 2019 and will be reviewed in a minimum period of four years (2023) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

A. Screening and Referral

- Screening mammography may be performed biennially in women aged 50 - 74 years in the general population.
- For women of high risk of breast cancer, where no genetic variant has been identified, screening mammography may be considered from 30 - 39 years of age, performed annually from 40 - 59 and biennial from 60 onwards.
- For carriers of pathogenic or likely pathogenic variants in BRCA1, BRCA2 and PALB2, annual magnetic resonance imaging should be offered from 30 - 49 years of age, annual mammography from 40 - 69 and biennial mammography from 70 onwards.
- Patients with any of the following conditions should be referred early (within two weeks) to breast or surgical clinic for further evaluation:
  - women aged >35 years with signs and symptoms
  - high risk group with signs and symptoms
  - patients with clinical signs of malignancy

B. Assessment and Diagnosis

- Breast Imaging Reporting and Data System (BI-RADS®) is the preferred reporting method in the management of breast cancer.
- Minimally invasive biopsy technique (MIBT) with core needle is the preferred diagnostic technique for both palpable and non-palpable breast lesions.
- Repeat image-guided MIBT or consider surgical excision when the initial core biopsy results are non-diagnostic or discordant with the imaging findings.
- Estrogen and progesterone receptors status should be assessed in all cases of breast cancer.
- Human Epidermal Growth Factor Receptor 2 (HER2) test using immunohistochemistry should be performed on all invasive breast cancer specimens.
- In-situ hybridisation test should be done only in equivocal HER2 (immunohistochemistry 2+) on invasive breast cancer specimens.
- Patients with early breast cancer and:
  - asymptomatic, routine imaging screening for metastasis should not be performed

- with signs and symptoms of lung, liver and bone metastases, or abnormal related laboratory tests, the routine imaging investigations should be performed
- with localised bone pain, elevated alkaline phosphatase or symptoms suggestive of bone metastases, bone scintigraphy should be used if plain radiography or computed tomography staging is negative

- Patients with locally advanced and advanced breast cancer, imaging modalities e.g. computed tomography, bone scintigraphy, magnetic resonance imaging or positron emission tomography/computerised tomography should be done to assess the extent of disease depending on the indications.

C. Treatment

- Multidisciplinary team approach should be considered in the management of breast cancer to improve clinical outcomes.
- In women treated with breast conserving surgery for ductal carcinoma in situ of <2 mm margin, the benefits and risks of further treatment (surgery or radiotherapy) should be discussed to reduce the risk of local recurrence.
- In early breast cancer patients with clinically lymph nodes negative who have breast conserving surgery and sentinel lymph nodes (SLNs) biopsy, no further axillary treatment is needed in two or less positive SLNs.
- In early breast cancer patients with clinically lymph nodes negative who have mastectomy and SLNs biopsy with two or less positive SLNs, axillary treatment either radiotherapy or surgery should be offered.
- Neoadjuvant chemotherapy may be offered to patients with triple negative or HER2-positive early breast cancer to enable breast conserving surgery but its benefits and risks need to be discussed with the patients.
- Neoadjuvant endocrine therapy, preferably aromatase inhibitors, may be considered in post-menopausal women with hormone-receptor positive breast cancer who are not suitable for chemotherapy.
- Chemotherapy and trastuzumab-based therapy should be offered to patients with HER2-positive breast cancer who require neoadjuvant therapy.
- Adjuvant extended endocrine therapy may be offered to hormone receptor-positive breast cancer based on the individual's risk of disease recurrence and potential side effects.
- Trastuzumab should be given to women with HER2-positive breast cancer having adjuvant chemotherapy.

- Endocrine therapy should be considered as first-line treatment in hormone-receptor positive, HER2-negative metastatic breast cancer unless there is evidence of visceral crisis or endocrine resistance.
- Bisphosphanates may be offered in breast cancer patients with bone metastases to reduce skeletal-related events.
- All patients with invasive breast cancer who have breast conserving surgery with clear margin should be offered adjuvant radiotherapy.
- Adjuvant radiotherapy should be offered to the following post-mastectomy breast cancer patients with:
  - one or more positive lymph nodes
  - positive margin not amenable for surgery
- Adjuvant radiotherapy should be considered in node negative T3 or T4 breast cancer.

D. Fertility Preservation

- Fertility preservation should be discussed with all breast cancer patients in the reproductive age group and suitable patients should be referred to fertility specialist.

E. Familial Breast Cancer

- Intensive screening of BRCA carriers and high risk individuals should be vigilantly performed and adhered to recommended guidelines.
- Risk-reducing surgeries should be discussed and offered to women with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 genes.

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) 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

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

The CPG update was done based on the first edition of evidence-based CPG on Management of Breast Cancer (Second Edition), issued in 2010. In the update, certain methodology was used e.g. GRADE principles while the scope on assessment and diagnosis, treatment and familial breast cancer was expanded. A chapter on fertility preservation was also introduced. A literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published in the last four years, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted from 23 November 2017 to 6 January 2018. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2019 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were made to other CPGs on Breast Cancer e.g.

- Early and locally advanced breast cancer: diagnosis and management [National Institute for Health and Clinical Excellence (NICE), 2018]
- Familial breast cancer: classification care and managing breast cancer and related risks in people with a family history of breast cancer (NICE, 2018)
- Treatment of primary breast cancer (Scottish Intercollegiate Guideline Network, 2013)
- Breast Cancer Version 1.2019 [National Comprehensive Cancer Network (NCCN), 2019]

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as references.

A total of 33 clinical questions were developed under eight different sections (risk factors, screening, referral, assessment/diagnosis, staging, treatment, survivorship programme and familial breast

cancer). Members of the DG were assigned individual questions within eight sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 26 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG strictly follows the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid-634).

OBJECTIVES

The objectives of the CPG are to provide recommendations on the management of breast cancer on following aspects:

- screening and referral
- diagnosis and assessment
- treatment and follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2.**

TARGET POPULATION

a. Inclusion Criteria

- Patients with early, advanced and metastatic breast carcinoma
- Individuals with increased risk of breast carcinoma

b. Exclusion Criteria

- Non-epithelial breast malignancy

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of breast cancer including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policy makers
v. patients and their advocates
vi. professional societies

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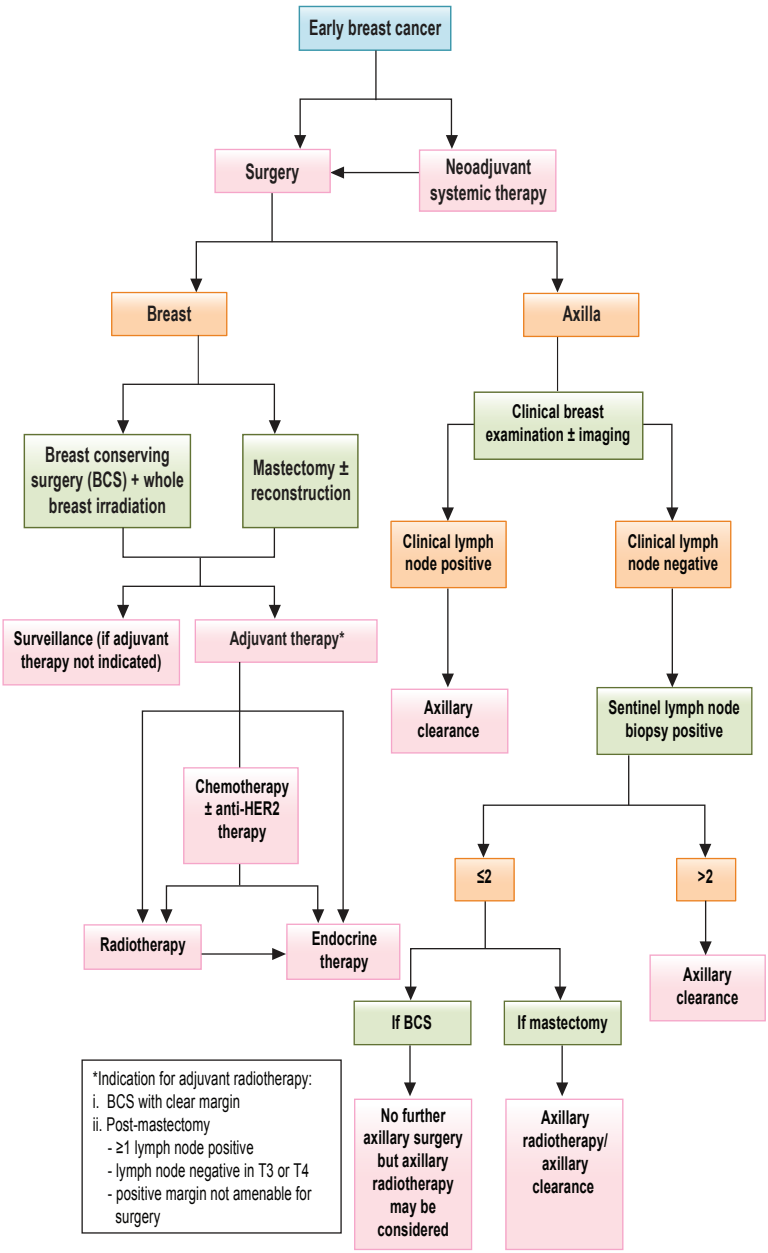
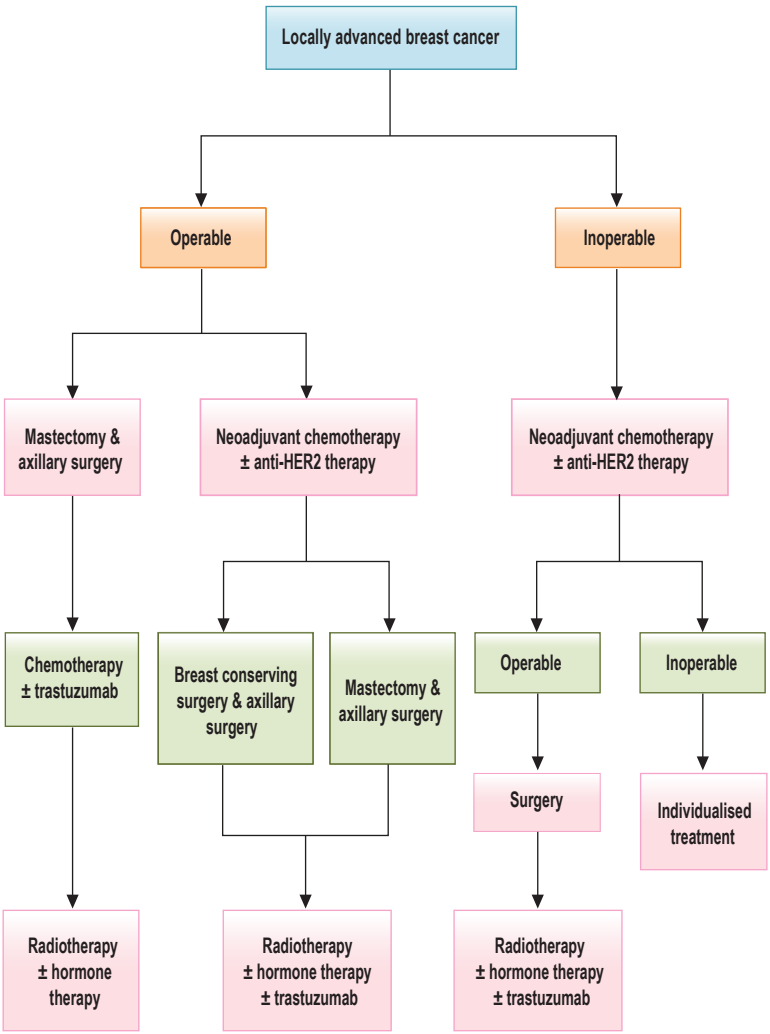
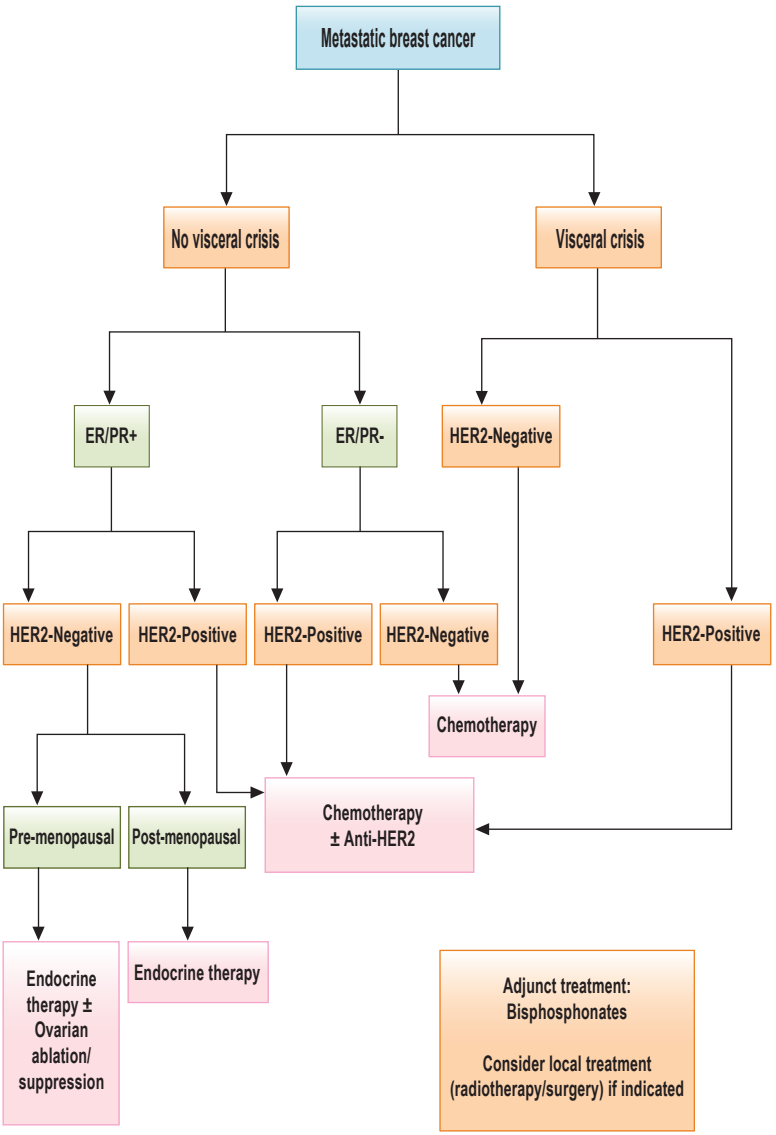
ALGORITHM 1. MANAGEMENT OF EARLY BREAST CANCER



ALGORITHM 2. MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER



ALGORITHM 3. MANAGEMENT OF METASTATIC BREAST CANCER



1. INTRODUCTION

Breast cancer is the most important cancer among women worldwide including in Malaysia. Regardless of gender, breast cancer contributed to 19.0% of all new cancer cases diagnosed in 2012 - 2016 compared with 17.7% in 2007 - 2011. The new cases of breast cancer had increased from 32.1% to 34.1% of overall cancer among women in similar period of comparison which gave a 2% increment. The Age-Standardised Incidence Rate (ASR) had increased to 34.1 per 100,000 populations in 2012 - 2016 from 31.1 per 100,000 population in 2007 - 2011. The incidence started to increase at the age of 25 and peaked at the age of 60 to 64 years. Refer to **Table 1** and **Figure 1**. The incidence was highest among Chinese (40.7 per 100,000) followed by Indian (38.1 per 100,000) and Malay (31.5 per 100.000). The overall lifetime risk was 1 in 27, with 1 in 22 for Chinese, 1 in 23 for Indians and 1 in 30 for Malays.[1, level III]

Table 1. Female breast cancer incidence by year in Malaysia

All residents	Number	Crude rate	ASR	Cumulative Risk
2007 - 2011	18, 206	28.6	31.1	3.4
2012 - 2016	21, 634	32.5	34.1	3.7
2012	4, 266	32.1	33.5	3.6
2013	4, 076	30.2	31.0	3.4
2014	4, 150	30.8	31.7	3.5
2015	4, 518	33.0	33.4	3.6
2016	4, 626	33.8	34.4	3.8

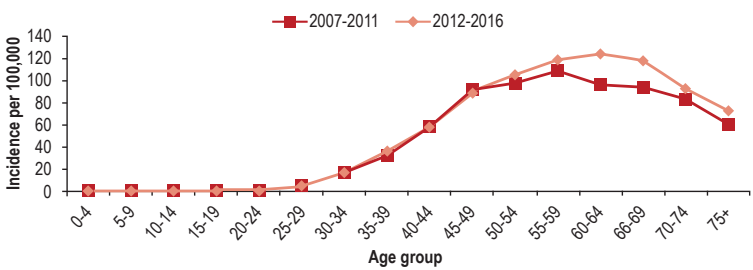


Figure 1. Female breast cancer: comparison of age-specific incidence rate by year in Malaysia

At diagnosis, 52.1% of the cases were diagnosed at early stage (stage I and II) with mainly at stage II (34.5%). However, the percentage of late diagnosis (stage III and IV) in the country had increased from 43.2% in 2007 - 2011 to 47.9% in 2012 - 2016 (refer to **Figure 2**).[1, level III]

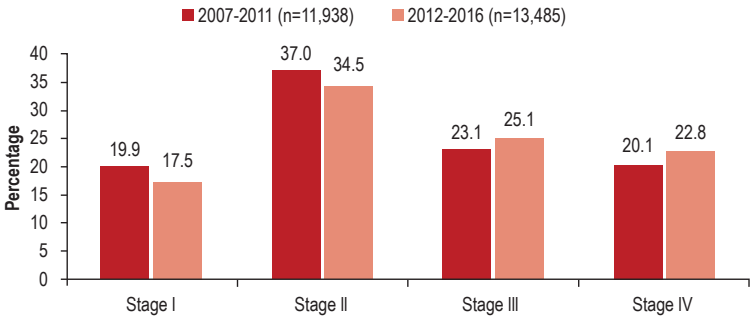


Figure 2. Female breast cancer: comparison of staging percentage by year in Malaysia

The overall 5-year relative survival (RS) for breast cancer is 66.8%. Stage I and II breast cancer at diagnosis have a better relative survival, being above 80% up to 10 years for Stage 1 and five years for Stage II. However, it deteriorates faster for Stage III and IV. By ethnicity, Chinese had the highest RS followed by Indians and Malays. International comparison with selected countries in Asia, the 5-year RS in Malaysia is higher than India and Thailand but lower than Singapore, China, Korea and Japan.[2, level II-2]

Early diagnosis improves cancer outcomes by provision of effective treatment, at lower cost and with less complex interventions. The principles to achieve early diagnosis are relevant at all healthcare levels. These are:[3]

- awareness of cancer symptoms and accessing care
- clinical evaluation, diagnosis and staging
- access to treatment

Over the years, many advancements in the management strategy are observed including screening method, early diagnosis and treatment modalities. Different strategies of breast cancer classification and staging have evolved over the years. Intrinsic (molecular) subtyping is essential in clinical trials and well understanding of the disease. Many technologies are being developed to detect distant metastasis and recurrent disease as well as to assess response to treatment. Advances in molecular biology and pharmacology aids in better understanding of breast cancer, enabling the design of effective therapy to target the cancer and responds efficiently.

In view of the above findings, it is timely to update the CPG on Management of Breast Cancer (Second Edition) to guide healthcare providers in the management of the disease based on latest available evidence.

2. RISK FACTOR

The cause of the vast majority of breast cancers remains unknown. However, a number of risk factors has been established and can be divided into non-modifiable and modifiable groups.

2.1 Non-modifiable

- **Age**

  The risk of breast cancer increases with age.[26] Based on latest National Cancer Registry Report of Malaysia, the incidence started to increase at the age of 25 and peaked at the age of 60 to 64 years.[1]

- **Gender**

  Female has much higher risk of breast cancer compared with male.[4]

- **Family history**

  The risk for breast cancer increases in women with family history of breast cancer at young age and being a carrier of pathogenic or likely pathogenic variants in e.g. BRCA1, BRCA2, PALB2, ATM and CHEK2.[5] Refer to **Chapter 8** on **Familial Breast Cancer**.

- **Reproductive factors**

  Early menarche and late menopause are risk factors for breast cancer.[6, level II-2]

  - Young age at menarche (≤12 years old) increases risk of luminal tumour (OR=1.39, 95%CI 1.23 to 1.57).
  - Late menopause (≥50 years old) increases risk of luminal tumour (OR=1.15, 95% CI 1.0 to 1.32) and Estrogen Receptor Negative (ER-)/Progesterone Receptor Negative (PR-) tumour (OR=1.19, 95% CI 1.00 to 1.43). Refer to **Table 2**.

- **History of neoplastic disease of the breast**

  - Patients with previous history of breast cancer carry an elevated risk of developing new primary breast cancer.[4]
  - Patients with breast carcinoma in situ are at high risk to develop invasive breast carcinoma.[4]
  - Patients with atypical ductal hyperplasia and lobular hyperplasia (atypical lobular hyperplasia and lobular carcinoma in-situ), have clinically significant increased risk of developing breast cancer.[7, level III]

- **Breast density**

  The risk of breast cancer increases two times in scattered fibroglandular density [Breast Imaging Reporting and Data System (BI-RADS®) b] and four times in an extremely dense breast (BI-RADS® d).[4]

Absolute non-dense area (BI-RADS® a) reduces the risk of breast cancer in pre-menopausal (OR=0.82, 95% CI 0.71 to 0.94) and post-menopausal (OR=0.85, 95% CI 0.75 to 0.96) women.[8, level II-2]

Refer to **Appendix 3** on Recommended Reporting System (Breast Composition Illustrations).

2.2 Modifiable

- **Reproductive factors**

  Nulliparity and lack of breastfeeding are risk factors for breast cancer.[6, level II-2]
  - Nulliparity increases risk of luminal tumour (OR=1.26, 95% CI 1.11 to 1.44).
  - Lack of breastfeeding history increases the risk of all molecular subtypes, $OR_{luminal}$=1.35 (95% CI 1.05 to 1.74), $OR_{HER2\ enriched}$=1.97 (95% CI 1.39 to 2.80) and $OR_{triple\text{-}negative}$=1.85 (95%CI 1.06 to 3.21).
  - Older age at first live childbirth increases the risk of breast cancer.[26]

- **Hormonal factors**
  - Oral contraceptives (OC) have a small risk of breast cancer (OR=1.521, 95% CI 1.25 to 1.85).[9, level II-2]
  - Current OC use (HR=1.36, 95% CI 1.09 to 1.71), ≥10 years duration of OC use (HR=1.29, 95% CI 1.09 to 1.54) and <10 years since last use (HR=1.36, 95% CI 1.15 to 1.61) are associated with pre-menopausal breast cancer.[10, level II-2]
  - Progestogen OC use ≥5 years is associated with Estrogen Receptor Positive (ER+) breast cancer (HR=1.59, 95% CI 1.09 to 2.32).[10, level II-2]
  - Combination hormone replacement therapy has a mild risk for breast cancer.[4]
  - Unopposed oestrogen use in hysterectomised women mildly increases the risk of breast cancer and only after longer term use (>15 years).[4]

- **Lifestyle**
  - Being overweight or obese throughout adulthood increases the risk of post-menopausal breast cancer.[163]
  - Physical activity measured in metabolic equivalent of task (MET) minutes/week shows dose-dependent effect on risk of breast cancer. The higher the MET, the lower the risk as shown below.[11, level II-2]

Physical activity in MET minutes/week	Pooled RR (95% CI) of breast cancer
<600	Reference
600 - 3999 (low active)	0.967 (0.937 to 0.998)
4000 - 7999 (moderately active)	0.941 (0.904 to 0.981)
≥8000 (highly active)	0.863 (0.829 to 0.900)

- World Health Organization (WHO) recommends at least 600 MET minutes of total activity (irrespective of domains) per week for health benefits; e.g. about 150 minutes/week of brisk walking or 75 minutes/week of running

  - Regular (≥3 cups per day) of green tea consumption is associated with a decreased risk of breast cancer in Chinese females (OR=0.79, 95% CI 0.65 to 0.95).[12, level II-2]
  - Consumption of ≥2 cups of coffee per day reduces breast cancer risk but nonsignificant (RR=0.98, 95% CI 0.97 to 1.00).[13, level II-2]
  - A dietary folate intake has no effect on risk of breast cancer (RR=0.98, 95% CI 0.90 to 1.05).[14, level II-2]
  - Among pre- and post-menopausal women, soy isoflavone intake reduces breast cancer risk with OR of 0.74 (95% CI 0.64 to 0.85) and 0.75 (95% CI 0.63 to 0.86) respectively.[15, level II-2]
  - Alcohol (especially beer) consumed more than 10 g/day especially among post-menopausal women is a risk factor for developing invasive breast cancer.[4]

- **Radiation exposure**
  - Multiple exposures of therapeutic radiation to the chest for cancer at an early age e.g. Hodgkin's disease pose a high risk of developing breast cancer.[4]
  - Radiotherapy (RT) for breast cancer treatment increases risk of contralateral breast cancer.[4]

3. SCREENING

Screening for breast cancer is performed in individuals without any signs or symptoms of the disease for early detection and best chance of survival.

Although breast self-examination is not a screening method, it is advocated to raise awareness of breast cancer and empower women to take responsibility of their own health.[4] Clinical breast examination (CBE) is an important component of clinical encounter to maximise the earliest detection of palpable cancers.[26] As the incidence of breast cancer in Malaysia increases at the age of 35 years,[1] CBE is advocated to be initiated from this age.

In women of European descent, a number of risk assessment tools [e.g. Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), Gail, Tyrer Cuzick] have been built using predominantly lifestyle factors and family history of cancers in order to estimate an individual woman's risk of breast cancer. For example, NICE recommends unaffected women aged 35 years and older and with no physical symptoms of breast cancer may be stratified into four categories using BOADICEA risk assessment tool for the purpose of screening recommendations:[5]

- average risk (<17% lifetime risk)
- moderate risk (>17% but <30% lifetime risk)
- high risk (>30% lifetime risk but no known genetic variant)
- high risk carriers of pathogenic/likely pathogenic variants

Whilst the above tools are accurate for the population, they are less useful for individual risk prediction. Notably, these tools generally overestimate risk in the Asian population and ongoing efforts seek to improve risk assessment for the Asian population by including genetic factors and/or mammographic density.

In a local health technology assessment on various risk assessment tools, the Gail model was shown to have good calibration and moderate discriminative ability. However, it was not suitable to be introduced as one of the strategies in the prevention of breast cancer under the Malaysian National Cancer Control Programme yet as it needs further validation to develop a well-fitted model that would have better predictive ability tailored to Malaysian population. In addition, this model needs continual validation to determine the consistency of its performance.[16, level I]

3.1 Screening of Unaffected Women

Digital breast tomosynthesis (DBT) + full-field digital mammography (FFDM) yields higher detection rates of breast cancer lesion compared with FFDM alone in asymptomatic women.[17, level III]

The followings have been recommended for screening by the existing guidelines:

- For women with average risk, screening mammography may be performed every two years in those aged 50 - 74 years. Although not recommended, women aged 40 - 49 years may be considered for annual screening mammography after potential benefits and harms of the screening have been discussed, as well as on the their preference and breast cancer risk profile. Screening should be continued for those women aged 70 - 74 years as long as they are in a good health, expected to live 10 more years or longer and do not have severe co-morbid conditions that could limit their life expectancy.[138]
- For women of moderate risk, screening mammography may be performed annually from 40 - 49 years of age, annually or biennially from 50 - 59 and 3-yearly from 60 onwards.[5]
- For women of high risk, where no genetic variant has been identified, screening mammography may be considered from 30 - 39 years of age, performed annually from 40 - 59 and 3-yearly from 60 years onwards.[5]
- For carriers of pathogenic or likely pathogenic variants in BRCA1, BRCA2 and PALB2, annual magnetic resonance imaging (MRI) should be offered from 30 - 49 years of age, annual mammography from 40 - 69 and 3-yearly mammography from 70 onwards.[5]

Ultrasound as a complementary imaging may be considered after a mammography or breast MRI shows abnormality. It should not be used as a screening tool.

Refer to **Table 7** on **Summary of recommendations on screening for women with no personal history of breast cancer**.

3.2 Surveillance of Affected Women

For women with personal history of breast cancer and increased risk for recurrence or a second breast cancer, they should be offered yearly mammography of the remnant breast and the contralateral breast for five years. With regards of cost-effective strategy, NICE recommends the following screening in women with previous history of breast cancer:[5]

- For those aged 50 - 74 years and remain at high risk of breast cancer (including BRCA1 or BRCA2 mutation and do not have a TP53 mutation), annual mammographic surveillance should be offered.
- For those aged 30 - 49 years and remain at high risk of breast cancer including BRCA 1, BRCA2 or TP53 mutation, annual MRI surveillance should be offered.

- Consider annual MRI for women aged 20 - 69 years with a known TP53 mutation or those untested but have a greater than 30% probability of being TP53 carrier.

For those with personal history of breast cancer and dense breast tissue, or diagnosed before the age 50, annual surveillance with breast MRI is recommended.[18, level III]

Women who have received chest radiation before the age of 30, e.g. in Hodgkin lymphoma, are recommended to do annual breast MRI and mammography or digital breast tomosynthesis screening beginning at the age of 25 or eight years after radiation, whichever is later.[18, level III]

Women at high risk should make decision to start screening with health care providers, taking into accounts their personal circumstances and preferences.

- For local setting, breast cancer screening is based on the risk of developing the cancer:
  - general population - women with:[5]
    - no personal history of breast cancer
    - no strong family history of breast cancer
  - Individuals with high risk of developing breast cancer:[5;18, level III]
    - BRCA mutation
    - first-degree relatives of BRCA carrier who have not been tested
    - history of chest irradiation at young age
    - personal history(s) of breast cancer
    - strong family history of breast or ovarian cancer
      - first degree relatives: mother, father, siblings, children
      - second degree relatives: grandparents, aunties, uncles, nieces, nephews

Recommendation 1

- Screening mammography may be performed biennially in women aged 50 - 74 years in the general population.
- For women of moderate risk, screening mammography may be performed annually from 40 - 49 years of age, annually or biennially from 50 - 59 and biennially from 60 onwards.
- For women of high risk of breast cancer, where no genetic variant has been identified, screening mammography may be considered from 30 - 39 years of age, performed annually from 40 - 59 and biennially from 60 onwards.
- For carriers of pathogenic or likely pathogenic variants in BRCA1, BRCA2 and PALB2, annual MRI should be offered from 30 - 49 years of age, annual mammography from 40 - 69 and biennial mammography from 70 onwards.

*Refer to the yellow box above

4. REFERRAL

There is no retrievable evidence on the referral criteria of patients with signs and symptoms to breast clinic.

- Based on the consensus of CPG DG, the following conditions warrant early referral as early as possible (within two weeks) to breast clinic for further evaluation:
  - women aged >35 years with signs and symptoms*
  - high risk group with signs and symptoms*
  - patients with clinical signs and symptoms of malignancy*

*General signs and symptoms:
- palpable mass
- breast pain
- nipple discharge

Signs of malignancy:
- hard and fixed mass
- asymmetric thickening/nodularity
- skin changes
  - peau d'orange
  - erythema
  - nipple excoriation
  - scaling or eczema
  - skin ulcer
  - satellite skin nodule
- blood-stained nipple discharge
- axillary mass
- image-detected suspicious lesion

Recommendation 2
- Patients with any of the following conditions should be referred early (within two weeks) to breast or surgical clinic for further evaluation:
  - women aged >35 years with signs and symptoms*
  - high risk group with signs and symptoms*
  - patients with clinical signs of malignancy*

*Refer to the preceding text.

5. ASSESSMENT AND DIAGNOSIS

5.1 Triple Assessment

- Triple assessment which consists of clinical assessment, imaging [ultrasound (US) and/or mammography] and pathology (histology and/or cytology) is an established method for the diagnosis of breast cancer.[4]

5.1.1 Clinical

Adequate history taking to assess risk and thorough CBE are mandatory in breast cancer diagnosis. The degree of suspicion of breast cancer based on clinical breast examination is variable.

5.1.2 Imaging

a. Diagnostic accuracy of mammography combined with ultrasonography

Combined mammography and US assessment improve breast cancer detection in symptomatic women above 35 years old and thus should be offered in this group of patients. In women younger than 35 years old, US should be used as the initial imaging modality in triple assessment.[4]

b. Screening and diagnostic accuracy of digital breast tomosynthesis

DBT, also known as 3D mammography, is a new screening and diagnostic breast imaging tool to improve the early detection of breast cancer. There was strong evidence on this modality.

In a good meta-analysis on studies in Europe and United States of America, DBT + FFDM, compared to FFDM alone, yielded higher detection of breast cancer lesions in asymptomatic women:[17, level III]

- sensitivity - 90.77% (95% CI 80.70 to 96.51) vs 60.00% (95% CI 47.10 to 71.96)
- specificity - 96.49% (95% CI 96.04 to 96.90) vs 95.55% (95% CI 95.04 to 96.01)
- reduction in recall rate: difference= -27.6 per 1000 screens (95% CI -30.8 to -24.5)
- reduction of false positive rate: difference= -29.5 per 1000 screens (95% CI -32.9 to -26.4)

In another meta-analysis, results of pooled diagnostic studies showed significant incremental rate of 3.9 cancers (95% CI 2.7 to 5.1) per 1000 for DBT compared with FFDM.[19, level III] There was no quality assessment reported in the meta-analysis.

A meta-analysis of seven moderate quality studies showed DBT had a better diagnostic accuracy compared with FFDM for benign and malignant lesions in breasts. The pooled DOR of DBT was 26.04 (95% CI 8.70 to 77.95) compared with pooled DOR of 16.24 (95% CI 5.61 to 47.04) in DM.[20, level III]

A systematic review demonstrated the sensitivity of DBT ranging between 69% and 100% and specificity ranging between 54% and 100%. The overall quality of the primary papers was low, with a risk of bias and follow-up and limitations on applicability of the results.[21, level II-2]

Recommendation 3
- Digital breast tomosynthesis may be considered in screening and diagnosis of breast cancer based on its availability.

c. Adequate Imaging Reporting System

Breast Imaging Reporting and Data System (BI-RADS®) was established by the American College of Radiology (ACR) in 1993. It is designed to standardise breast imaging reporting and thus reduce variations in the imaging interpretation. This enables radiologists to communicate the findings, final assessment and recommendations on specific management to the referring physicians clearly and consistently. It also facilitates outcome monitoring and quality assessment.

BI-RADS® contains standardised terminology (descriptors) for mammography, breast US and MRI for use in daily practice. The ACR BI-RADS® Atlas 2013 is the updated version of the 2003 Atlas.[22, level III] Refer to **Appendix 3**. 'Borang Permohonan Pemeriksaan Radiologi' (Breast Imaging Survey Form) has been developed by MoH to be used in mammography reporting. Refer to **Appendix 4**.

Recommendation 4
- Breast Imaging Reporting and Data System (BI-RADS®) is the preferred reporting method in the management of breast cancer.

d. Accuracy of image-guided biopsy

All palpable masses should be imaged to see if there is discordance in clinical and imaging size. Any discordance should lead to image-guided biopsy and free hand biopsies should be avoided to ensure timely diagnosis.

Minimally invasive biopsy technique (MIBT) is the standard of care for diagnosing most breast lesions. Image-guided MIBT is recommended for both palpable and non-palpable lesions to increase accuracy of sampling. US, if available, is recommended in patients with palpable masses. If the lesion is non-palpable but visible sonographically, US-guidance optimises patient's comfort.[23, level III]

In all breast lesions, core needle biopsy or vacuum-assisted technique is preferable to fine needle aspiration cytology (FNAC) for better characterisation of tumour type, marker analysis and immunohistochemistry.[23, level III]

Pathology and imaging concordance by MIBT shows a success rate of 90% or greater.[23, level III]

e. Management of discordance lesion

Repeat image-guided percutaneous core or vacuum-assisted needle biopsy sampling is an alternative when the initial core biopsy results are non-diagnostic or discordant with the imaging findings. Another alternative is surgical excision.[24, level III]

Recommendation 5

- Minimally invasive biopsy technique (MIBT) with core needle is the preferred diagnostic technique for both palpable and non-palpable breast lesions.
- Repeat image-guided MIBT or consider surgical excision when the initial core biopsy results are non-diagnostic or discordant with the imaging findings.

f. Role of magnetic resonance imaging

MRI may be considered in the following clinical situations in breast cancer:[4; 18, level III; 25; 26]

- invasive lobular cancer
- LCIS
- suspicion of multicentricity
- genetic high risk
- occult disease (T0 N+/M+ disease) - refer to **Appendix 5** on **TNM Classification**
- Paget's disease without routine radiological evidence of underlying tumour
- breast implants/foreign bodies
- diagnosis of recurrence in previous breast reconstruction
- follow-up after neo-adjuvant therapy
- dense breasts
- pre-operative planning in breast-conserving surgery (BCS)

Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.[26]

5.1.3 Laboratory Investigation

a. Histopathological examination

- Core needle biopsy has become a well-established tool for diagnosing both palpable and non-palpable breast lesions. It is considered as part of triple assessment of breast disease.
- If core needle biopsy is not available, FNAC may be considered for pathological assessment of palpable breast lumps. In equivocal FNAC, core biopsy should be performed for pathological diagnosis.

Adequate surgical pathology reporting of breast cancer using standard proforma with minimum dataset should have:

- maximum diameter of invasive tumour
- location (side and quadrant), multifocality (presence of ≥2 foci of cancer within the same breast quadrant)/multicentricity (presence of ≥2 foci of cancer in different quadrants of the same breast)
- tumour type (histology according to WHO classification)
- histological grade
- lymph node involvement and total number of nodes examined
- resection margins
- lymphovascular invasion
- non-neoplastic breast changes
- hormone receptor status: ER/PR
- Human Epidermal Growth Factor Receptor 2 (HER2)/c-erb B2 assessment

Refer to **Appendix 6** on Histopathology Worksheet for Breast Biopsy/ Mastectomy.

- ER and PR receptor status should be assessed in all breast cancer and cancer recurrence to determine the benefits of endocrine therapy. Positive interpretation requires at least 1% of tumour cells showing positive nuclear staining of any intensity. Receptor negative is reported if <1% of tumour cells show staining of any intensity.[27, level III]

b. Human Epidermal Growth Factor Receptor 2 Test

HER2 is a trans-membrane epidermal growth factor receptor that plays an important role in tumour growth signalling pathway of breast cancer. Assessment of HER2 status is essential to establish prognosis and to determine patient eligibility for HER2 targeted therapy.

HER2 testing may be performed by various methods including immunohistochemistry (IHC), fluorescent in-situ hybridisation (FISH), chromogenic in-situ hybridisation (CISH) and silver-enhanced in-situ hybridisation (SISH).[4] The quality of HER2 testing encompasses tissue

handling process from the operating theatre to the laboratory, testing protocols, scoring and interpretation of results.

HER2 test using immunohistochemistry should be performed on all invasive breast cancer specimens.[4] HER2 status can be accurately assessed in core needle biopsy [sensitivity of 93% (95% CI 80.94% to 98.5%) and specificity of 99.9% (95%CI 98.05% to 100%)].[28, level III]

NICE recommends that request the ER, PR and HER2 status of all invasive breast cancers simultaneously at the time of initial histopathological diagnosis.[25]

- If the IHC result is 3+, diagnosis is HER2 positive. If the result is 0 to 1+, diagnosis is HER2 negative.

In equivocal HER2 (IHC 2+, weak to moderate complete membrane staining observed in >10% of tumour cells), American Society of Clinical Oncology/College of American Pathologists recommends in-situ hybridisation (ISH) reflex test using the same specimen or a new specimen if available.[29]

Recommendation 6

- Estrogen and progesterone receptors status should be assessed in all cases of breast cancer.
- Human Epidermal Growth Factor Receptor 2 (HER2) test using immunohistochemistry should be performed on all invasive breast cancer specimens.
- In-situ hybridisation test should be done only in equivocal HER2 (immunohistochemistry 2+) on invasive breast cancer specimens.

Histopathologic features suggestive of possible HER2 test discordance and actions to be taken are shown in the table below.

Table 2. Histopathologic Features Suggestive of Possible HER2 Test Discordance

Criteria to consider if there are concerns regarding discordance with apparent histopathologic findings and possible false-negative or false-positive HER2 test result.
A new HER2 test should not be ordered if the following histopathologic findings occur and the initial HER2 test was negative: • Histologic grade 1 carcinoma of the following types: o Infiltrating ductal or lobular carcinoma, ER and PR positive o Tubular (at least 90% pure) o Mucinous (at least 90% pure) o Cribriform (at least 90% pure) o Adenoid cystic carcinoma (90% pure) and often triple negative
Similarly, a new HER2 test should be ordered if the following histopathologic findings occur and the initial HER2 test was positive: • Histologic grade 1 carcinoma of the following types: o Infiltrating ductal or lobular carcinoma, ER and PR positive o Tubular (at least 90% pure) o Mucinous (at least 90% pure) o Cribriform (at least 90% pure) o Adenoid cystic carcinoma (90% pure) and often triple negative
If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen if one of the following is observed: • Tumour is grade 3 • Amount of invasive tumour in the core biopsy specimen is small • Resection specimen contains high-grade carcinoma that is morphologically distinct from that in the core • Core biopsy result is equivocal for HER2 after testing by both ISH and IHC • There is doubt about the handling of the core biopsy specimen (long is chaemic time, short time in fixative, different fixative) or the test is suspected

Source: Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-2122

c. Accuracy of Ki67 as a predictor and prognostic marker

Ki67 (anti-MIB-1) has emerged as an immunohistochemistry test to detect proliferative index of tumours.

In a cohort study on early breast cancer, high Ki67 predicted outcome for all measures:[30, level II-2]

- ipsilateral breast tumour recurrence/IBTR (HR=3.126, 95% CI 1.390 to 7.029)
- loco-regional recurrence/LRR (HR=3.759, 95% CI 1.923 to 7.340)
- distant metastasis-free survival/DMFS (HR=3.436, 95% CI 1.926 to 6.130)

- breast cancer-specific survival/BCSS (HR=4.948, 95% CI 2.530 to 9.674)

Ki67 was also able to reclassify luminal subtype from Luminal A (LA) to Luminal B (LB). The LB subtype independently predicted:

- LRR (HR=3.612, 95% CI 1.555 to 8.340)
- DMFS (HR=3.023, 95% CI 1.501 to 6.087)
- BCSS (HR=3.617, 95% CI 1.629 to 8.031)

However, it did not predict IBTR (HR=2.483, 95% CI 0.982 to 6.281).

Contradictory, in another study on early breast cancer after BCS, Ki-67 did not predict overall survival (OS), cause-specific survival, local relapse-free survival, DMFS, recurrence-free survival and loco-regional recurrence-free survival ($p>0.05$).[31, level II-2]

A more recent cohort study on LB node negative breast cancer showed that low Ki67 score (<14%) significantly predicted a lower rate of relapse (9%) compared with high Ki67 score (≥14%) with a rate of relapse (18%).[32, level II-2]

The limitation in all three studies above is that blinding was not mentioned in the methodology.

- Lack of consistency in method and interpretation across laboratories limits Ki67 value. Contradicting evidence warrants better studies to address the clinical utility of Ki67. Thus, the use of Ki67 is based on clinician's discretion.

- **Molecular subtypes of breast cancer detected by immunohistochemistry**

According to the 2011 St. Gallen consensus conference, there are five breast cancer molecular subtypes based on the presence of receptors on the tumour cells and Ki67 proliferative index. Refer to **Table 3**.

Table 3. St. Gallen classification (2011): Definition of subtypes of breast cancer

Molecular subtypes of breast cancer	ER and PR (IHC)	HER2 (IHC/ISH)	Ki67 (IHC)
Luminal A	ER+ and/or PR+	HER2-	Ki67 <14%
Luminal B with HER2 negative	ER+ and/or PR+	HER2-	Ki67 ≥14%
Luminal B with HER2 positive	ER+ and/or PR+	HER2+	Any Ki67
HER2 enriched	ER-, PR-	HER2+	Any Ki67
Basal-like (triple negative)*	ER-, PR-	HER2-	Any Ki67

*May be CK5/6 + and/or EGFR+

Source: Falck AK, Fernö M, Bendahl PO, et al. St Gallen molecular subtypes in primary breast cancer and matched lymph node metastases--aspects on distribution and prognosis for patients with luminal A tumours: results from a prospective randomised trial. BMC Cancer. 2013;13:558

5.2 Staging

- The staging is based on current The American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th Edition).[33, level III] Refer to **Appendix 5** for further details.

5.2.1 Early breast cancer

In patients with asymptomatic early breast cancer (including ductal carcinoma in situ, stage I, stage IIA and stage IIB), imaging screening [chest radiograph, bone scan, liver ultrasonography and computerised tomography (CT) scan] for metastasis should not routinely be performed.[4] There is no latest update on imaging investigations in this group of patients.

However, in patients with signs and symptoms of lung, liver and bone diseases, or abnormal related laboratory tests, the above imaging investigations should be performed. A bone scan is indicated in patients presenting with localised bone pain or elevated alkaline phosphatase if sites are not imaged or visualised by plain radiograph or CT scan.[4]

NCCN and NICE give similar recommendations as above.[25; 26]

Recommendation 7
- Patients with early breast cancer and:
  - asymptomatic, routine imaging screening* for metastasis should not be performed
  - with signs and symptoms of lung, liver and bone metastases, or abnormal related laboratory tests, routine imaging investigations should be performed
  - with localised bone pain, elevated alkaline phosphatase or symptoms suggestive of bone metastases, bone scintigraphy should be used if plain radiography or computed tomography staging is negative

*Refer to the preceding text.

5.2.2 Locally Advanced Breast Cancer (Stage III)

In locally advanced breast cancer (LABC), more imaging should be done for staging. This includes CT scan, bone scintigraphy, MRI and positron emission tomography/computerised tomography (PET/CT).[25; 26]

- LABC is cancer that has not spread beyond the breast or to other parts of the body. This includes:[34, level III]
  - large breast tumours (>5 cm in diameter)
  - cancers that involve skin of the breast or underlying chest wall muscles
  - cancers that involve multiple ipsilateral axillary, internal mammary or infra/supra-clavicular lymph nodes
  - inflammatory breast cancer

5.2.3 Advanced (Metastatic) Breast Cancer (Stage IV)

In advanced (metastatic) breast cancer similar imaging as in Section 5.2.2 should be done for assessment of bony and visceral metastases.[25; 26]

Recommendation 8
- Patients with locally advanced and advanced breast cancer, imaging modalities e.g. computed tomography, bone scintigraphy, magnetic resonance imaging or positron emission tomography/computerised tomography should be done to assess the extent of disease depending on the indications.

Most malignant tumours have a higher glucose metabolism than normal tissue and thus take up more (^{18}F)-fluorodeoxyglucose PET (^{18}FDG PET). With computed tomography (CT), functional information can be assessed anatomically.[4]

The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II or operable III (T3N1) breast cancer. The recommendation against the use of PET scanning is supported by:[26]

- high false-negative rate in the detection of lesions that are small (<1 cm) and/or low grade
- low sensitivity for detection of axillary nodal metastases
- low prior probability of having detectable metastatic disease
- high rate of false-positive scans

^{18}FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.[26]

A good meta-analysis showed that ^{18}FDG PET/CT had excellent diagnostic performance compared with conventional imaging (CT thorax, abdomen and pelvis) for diagnosis of distant metastases in breast cancer:[35, level III]

- Pooled sensitivity for ^{18}FDG-PET/CT was 0.97 (95% CI 0.84 to 0.99) and specificity 0.95 (95% CI 0.93 to 0.97)
- Pooled sensitivity for conventional imaging was 0.56 (95% CI 0.38 to 0.74) and specificity 0.91 (95% CI 0.78 to 0.97)

In another meta-analysis, ^{18}FDG PET/CT showed better performance compared with bone scintigraphy for the detection of bone metastases in breast cancer:[36, level III]

- ^{18}FDG PET-CT: sensitivity of 0.93 (95% CI 0.82 and 0.98) and specificity of 0.99 (95% CI 0.95 to 1.00)
- Bone scintigraphy, sensitivity of 0.81 (95% CI 0.58 to 0.93) and specificity 0.96 (95% CI 0.76 to 1.00)

Recommendation 9

- (^{18}F)-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET) may be considered when standard imaging studies are equivocal or suspicious in locally advanced or metastatic disease.

6. TREATMENT

6.1 Multi-Disciplinary Team

Multidisciplinary team (MDT) meetings provide an opportunity to multiple specialties to collaboratively integrate diagnoses and treatment decisions for breast cancer patients. Members of MDT for breast cancer should consist of:

- breast surgeon
- radiologist
- pathologist
- oncologist
- breast care nurse

Other relevant healthcare providers (e.g. anaesthetist, plastic surgeon, radiotherapist, geneticist, gynaecologist, social worker etc.) may be involved when required.

The objective of MDT meetings is to improve patient care and treatment outcomes by achieving consensus among all participating specialists after considering all data and findings from those involved. It has been shown to reduce mortality of breast cancer by 18% (HR=0.82, 95% CI 0.74 to 0.91).[37, level II-2]

Recommendation 10

- Multidisciplinary team approach should be considered in the management of breast cancer to improve clinical outcomes.

6.2 Surgery

6.2.1 Early breast cancer

a. Adequate tumour-free margin in breast-conserving surgery

i. Invasive carcinoma

BCS with negative margin followed by adjuvant RT is an effective local treatment in treating early breast cancer. However, the extent of the negative margin remains controversial.

In a meta-analysis involving 33 studies on stage I and II invasive breast carcinoma, a two-fold increase in IBTR (OR=2.44, 95% CI 1.97 to 3.03) was observed in patients with positive margins (ink on tumour) compared with negative margins following BCS. The median follow-up was 79.2 months. However, margins wider than “no ink on tumour” were not associated with lower incidence of IBTR.[38, level III]

The above findings were supported by another meta-analysis.[39, level III] However, the quality of primary papers in both meta-analyses was not well reported.

- No tumour at ink margin on histopathological examination is adequate for BCS in invasive breast carcinoma.

ii. Ductal carcinoma in situ

There is a variation in the definition of adequate margin for ductal carcinoma in situ (DCIS) following BCS in the range of 0 - 2 mm.[4; 25; 40; 41, level III; 42]

In a large retrospective cohort study on women with DCIS, treated with BCS without adjuvant RT, larger negative margins were significantly associated with a lower LR rate compared with positive margin i.e. tumour on ink (HR of 0.75, 0.58 and 0.31 for negative margin widths of ≤2 mm, >2 - 10 mm and >10 mm respectively). In those with negative margins of <2 mm and received RT, the LR rate was reduced with a HR of 0.29 (p<0.0001).[43, level II-2]

Similar outcome was reproduced in another study on DCIS patients who underwent BCS with a median follow-up of 8.7 years. There was no difference in LRR in those with a negative margin <2 mm and adjuvant RT compared with those having ≥2 mm without RT (HR=0.77, 95% CI 0.19 to 3.23).[44, level II-2]

Recommendation 11

- In women treated with breast conserving surgery for ductal carcinoma in situ of <2 mm margin, the benefits and risks of further treatment (surgery or radiotherapy) should be discussed to reduce the risk of local recurrence.

b. Treatment after sentinel lymph node biopsy

Axillary lymph nodes dissection (ALND) in early breast cancer with clinically node-negative patients has largely been abandoned. This is attributed to upper limb lymphoedema, paraesthesia, seroma and motor nerve injury risks from this procedure. Completion of axillary surgery is no longer standard practice for up to two positive sentinel lymph nodes (SLNs) based on two major phase III non-inferiority randomised clinical trials (RCTs) discussed below.

The American College of Surgeons Oncology Group Z0011 study was on cT1-T2N0 breast cancer patients who underwent breast conserving surgery (BCS) with up to two positive SLNs identified by frozen section, touch preparation or haematoxylin-eosin staining on tissue sections. It showed sentinel lymph nodes dissection (SLND) alone was not inferior in survival and local recurrence (LR) compared with SLND followed by ALND with the following findings:[45, level I]

- HR for OS=0.79 (90% CI 0.56 to 1.10)
- HR for disease free survival (DFS)=0.82 (95% CI 0.58 to 1.17)
- LR of 1.6% for SLND vs 3.1% for ALND (p=0.11)

The After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial involved cT1-T2N0 breast cancer patients who underwent either BCS or mastectomy with positive SLNs. The patients were randomised to either axillary dissection or axillary RT. ALND and axillary RT after a positive SLNs provided excellent and comparable axillary control [HR for OS was 1.17 (95% CI 0.85 to 1.63) and DFS 1.18 (95% CI 0.93 to1.51).[46, level I] In both studies, the surgical morbidities (lymphoedema, paraesthesia, wound infection and seromas) were higher in the ALND group.

The above findings were supported by a meta-analysis study on similar group of patients (which included the AMAROS trial) showing a HR of 1.09 (95% CI 0.75 to 1.43) for OS and 1.01 (95% CI 0.58 to 1.45) for DFS. Axillary recurrence rate (p>0.05) and lymphoedema was higher in the ALND group (23.2% vs 10.8%).[47, level I] The primary papers used were of low quality.

- Clinically lymph node negative referred to:
  - no evidence of axillary lymph node involvement on physical examination and imaging studies
  - negative on cyto/histopathology in case of a suspicious axillary lymph node

Recommendation 12
- In early breast cancer patients:
  - with clinically lymph nodes negative who have breast conserving surgery and sentinel lymph nodes (SLNs) biopsy, no further axillary surgery is needed in two or less positive SLNs but axillary radiotherapy may be considered
  - with clinically lymph nodes negative who have mastectomy and SLNs biopsy with two or less positive SLNs, axillary treatment either radiotherapy or surgery should be offered

6.2.2 Locally advanced breast cancer

According to NNCN guidelines, neoadjuvant systemic therapy is indicated in women with inoperable breast cancer. It can render inoperable cancer to resectable cancer.[26]

Recommendation 13
- Inoperable breast cancer should be referred for neoadjuvant systemic therapy prior to surgical intervention.

a. Breast conserving surgery following neoadjuvant systemic therapy

Neoadjuvant systemic therapy can increase rate of BCS and benefits in operable breast cancer with BCS intention.[26]

A meta-analysis showed no difference in LR and regional recurrence between BCS and mastectomy in LABC with good response to neo-adjuvant chemotherapy (NACT). However the DFS (OR=2.35 95% CI 1.84 to 3.01) and OS (OR=2.12 95% CI 1.51 to 2.98) were shown to be higher in BCS.[48, level II-2]

- BCS following neoadjuvant systemic therapy can be considered in suitable patients if expertise and facilities are available.

6.2.3 Timing for breast reconstruction (with or without prosthesis) in breast cancer requiring post-operative radiotherapy

Post-mastectomy radiation therapy (PMRT) has detrimental effect on the aesthetic outcome and associated with a higher complication rate following breast reconstruction (BR). In cases where PMRT is anticipated, the optimum timing and methods of BR need to be considered before the surgery.

When an immediate BR is intended, a two-stage implant-based reconstruction is recommended.[26; 41, level III; 49, level III] The first stage involves placement of tissue expander (TE) followed by expansion of the expander within 1 - 6 months. In the second stage, the TE can be exchanged with a permanent implant either prior or after radiation therapy.[26; 49, level III]

A recent systematic review involving 1,565 two-stage implant-based reconstructive surgeries showed no significant difference in implant failure rate between TE radiation and implant radiation. The infection rate was significantly higher in the former (21.03% vs 9.69%). In one of the primary papers used in the review, patients with TE radiation have the best aesthetic results compared with patients on permanent implant radiation (75.0 vs 67.6%, $p<0.01$) and lower rates of grade IV capsular contracture (1.22 vs 6.3%, $p<0.01$).[50, level II-2] However, there was no quality assessment of the primary papers including possible confounding mentioned in the systematic review.

In delayed reconstruction in a previously irradiated patient, an autologous tissue reconstruction is the preferred method.[26] Due to paucity of data, the optimum timing of autologous reconstruction in the setting of PMRT is still unknown.

Delayed reconstruction is associated with significantly lower risks of overall (OR=0.38, 95% CI 0.24 to 0.62) or major complications (OR=0.52, 95% CI 0.31 to 0.89) compared with immediate procedures.[51, level II-2]

6.2.4 Metastatic breast cancer

a. Surgery on primary tumour

Patients with stage IV breast cancer has poor prognosis with 5-year survival rate of 27%.[52, level III]

In a RCT, no benefits were observed between surgical resection and non-surgical intervention for primary tumour in metastatic breast carcinoma in terms of:[53, level I]

- OS (HR=0.691, 95% CI 0.358 to 1.333)
- time to distant progression (HR=0.598, 95% CI 0.343 to 1.043)
- time to loco-regional progression including breast and regional lymph nodes (HR=0.933, 95% CI 0.375 to 2.322)

The limitation of this evidence was it being under-powered.

A Cochrane systematic review showed no difference in OS between breast surgery plus systemic therapy and systemic therapy alone (HR=0.83, 95% CI 0.53 to 1.31) for primary tumour in metastatic breast cancer (MBC). However, local progression free survival (PFS) was improved (HR=0.22, 95% CI 0.08 to 0.57) but distant PFS was shorter (HR=1.42, 95% CI 1.08 to 1.86). It was not possible to make definitive conclusions on the benefits and risks of breast surgery for MBC in view of only two low quality RCTs were used in the review.[54, level I]

Surgery after initial systemic therapy may be considered in patients requiring palliation of symptoms or with impending complications e.g. fungating tumour, pain, bleeding and ulceration.[26]

- There is insufficient evidence to recommend surgical resection for primary tumour to improve survival in MBC. However, the decision for surgery is individualised for palliative intent.

b. Local treatment

i. Bone

Bone metastases in MBC have a more indolent behaviour compared to visceral metastases. Nevertheless, it may lead to debilitating skeletal-related events (SREs) e.g. bone pain, pathological fractures, cord compression and hypercalcemia.

Treatment options to prevent or delay SREs include RT, endocrine treatment, molecular targeted therapy and bisphosphonates.

RT can give adequate pain control in 75 - 85 % of patients even without analgesics. Surgical stabilisation or decompression followed by RT are usually indicated for long bone fracture and symptomatic spinal metastases.[55, level III]

Surgery for symptomatic thoraco-lumbar spinal metastases in breast carcinoma shows a 30-day mortality rate of 4.9%, a 3-month survival rate of 81.5 % and, improvement of neurological function and ambulation.[56, level II-2]

ii. Lung

There is limited evidence to establish a survival advantage of pulmonary metastasectomy. However, a cohort study showed that resection of lung metastases from breast cancer may offer survival benefit for patients with disease free interval >36 months (p=0.0007), unilateral pulmonary metastases (p=0.0267) and complete metastasectomy (p=0.0153).[57, level II-2]

iii. Liver

Treatments of liver metastasis are liver resection and local ablation (radio-frequency, thermal and cryo-ablation, etc.).

Systemic reviews found that liver resection for breast cancer liver metastasis offered survival advantage in carefully selected patients with isolated liver metastases and in those with well controlled minimal extra-hepatic disease. Liver resection carried low post-operative mortality rate if performed in large-volume hepatobiliary centres.[58 - 59, level III] The primary papers included in the reviews were of low quality.

In a study on breast cancer patients with <5 liver metastases with or without bone metastasis but no other metastasis, there was significantly better survival rates in those treated with liver resection compared with matched non-surgically treated individuals (chemo- or hormonal treatment).[60, level III]

A case-control study demonstrated no survival benefits in patients underwent hepatic resection or ablation for isolated breast cancer liver metastasis compared with patients receiving standard medical care.[61, level II-2]

iv. Brain

The surgical management of breast cancer with brain metastases is controversial as there is no strong evidence to date.

In local practice, surgery followed by brain RT is suggested in patients with single or small number of potentially resectable, brain metastases, having good performance status and with no or well-controlled other metastatic disease. Whole brain radiotherapy (WBRT) alone is reserved for patients with poor performance status and multiple unresectable metastases. However, stereotactic radiosurgery (SRS) or stereotactic fractionated radiotherapy (SRT) is becoming increasingly popular as an adjunctive treatment to surgery. It is a minimally invasive outpatient procedure which delivers high dose of radiation precisely to the tumour.

A retrospective cohort study which included breast carcinoma found that gross total resection with SRS was associated with reduced LR (HR=0.32, 95% CI 0.17 to 0.6) and longer OS (HR=0.6, 95% CI 0.39 to 0.91) compared with SRS alone in patients with limited number of large brain metastases (>4 cm^3 or 2 cm in diameter).[62, level II-2]

Recommendation 14
- An individualised treatment may be offered in selected patients with metastatic breast cancer.

6.2.5 Loco-regional recurrence

All patients with LRR should be managed by an MDT to discuss all suitable treatment options.

As there is no retrievable evidence on treatment for LRR in breast cancer, the treatment algorithm is based on NCCN guidelines as shown in **Figure 3**.

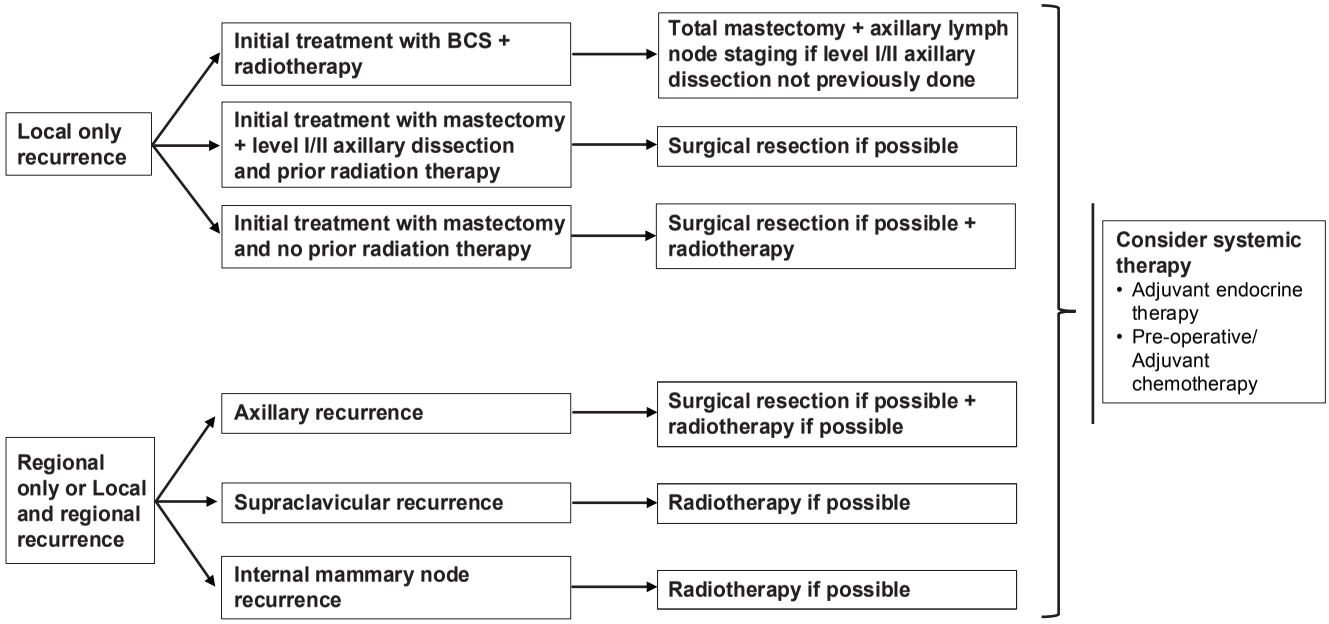


Figure 3. Treatment of local and regional recurrence

Adapted: National Comprehensive Cancer Network. Breast Cancer Version 1.2019. NCCN; 2019

The decision for further systemic therapy should be individualised based on factors e.g. tumour biology, previous treatment, length of disease-free interval and patient-related factors (co-morbidities, preferences, etc.).[63]

Recommendation 15
- An individualised approach should be offered in patients with loco-regional recurrent breast cancer.

6.3 Systemic Therapy
Refer to **Appendix 7 on Medications in Systemic Therapy of Breast Cancer and Their Common Side Effects**

6.3.1 Neoadjuvant therapy
Neoadjuvant therapy in breast cancer refers to the administration of treatment with the intent of downstaging the tumour and, improve operability and surgical outcomes.

a. Chemotherapy
For NACT in LABC, refer to **Section 6.2.2.a**.

For most patients with early breast cancer, chemotherapy is given following surgery. However, a meta-analysis showed that NACT can reduce tumour size leading to higher rate of BCS compared with adjuvant chemotherapy (64.8% vs 49.0%; RR=1.28, 95% CI 1.22 to 1.34). On the other hand, those receiving NACT had a higher rate of LR (21.4% vs 15.9%; RR=1.37, 95% CI 1.17 to 1.61). There was no difference in breast cancer mortality between the two groups (34.4% vs 33.7%; RR=1.06, 95% CI 0.95 to 1.18).[64, level I]

Not all cases will respond equally to NACT in early breast cancer. A meta-analysis showed that highest pathological complete response (pCR) rate to NACT was seen in triple negative tumour and HER2-positive tumour.[65, level I]

There was no quality assessment mentioned in both meta-analyses.

- Triple negative and HER2-positive tumours have increased frequencies of pCR response following NACT in early breast cancer.

Recommendation 16
- Neoadjuvant chemotherapy may be offered to patients with triple negative or HER2-positive early breast cancer to enable breast conserving surgery but its benefits and risks need to be discussed with the patients.

b. Endocrine therapy

The role of neoadjuvant endocrine therapy (NET) in breast cancer remains unclear due to concern of delayed time to clinical response compared with systemic chemotherapy. Thus, it is generally reserved for candidates who are unsuitable for chemotherapy or surgery.

A meta-analysis showed no significant differences between NET and neoadjuvant chemotherapy (NACT) in clinical response rate, radiological response rate, pathological response rate and BCS rate in ER+ breast cancer. The toxicity profile was significantly lower in the NET arm. However, these findings are based on two phase II RCTs and one phase III RCT which was terminated earlier due to poor accrual.[66, level I]

In a subgroup analysis of seven RCTs in the meta-analysis, increased clinical response rate (OR=1.69, 95% CI 1.36 to 2.10), radiological response rate (OR=1.49, 95% CI 1.18 to 1.89) and BCS rate (OR=1.62, 95% CI 1.24 to 2.12) were seen in aromatase inhibitors (AIs) compared with tamoxifen.[66, level I]

NICE recommends to consider NET for post-menopausal women with ER+ invasive breast cancer as an option to reduce tumour size if there is no definite indication for chemotherapy.[25]

Recommendation 17

- Neoadjuvant endocrine therapy, preferably aromatase inhibitors, may be considered in post-menopausal women with hormone-receptor positive breast cancer who are not suitable for chemotherapy.

c. Anti-HER2 therapy

HER2 is overexpressed in 15 - 20% of breast cancer and is associated with an aggressive clinical course of the disease.[67] It is well-known that patients diagnosed with HER2-positive breast cancer need to be treated with a combination of anti-HER2-directed therapy and chemotherapy in adjuvant setting. Evidence is emerging on its use in neoadjuvant setting as discussed below.

In 2011, a pooled analysis of two RCTs in patients with pathologically confirmed and untreated HER2-positive early breast cancer in neoadjuvant setting showed that the probability to achieve pCR was higher in the combined trastuzumab and chemotherapy group than in chemotherapy alone (RR=2.07, 95% CI 1.39 to 2.46). The relapse free rate was also in favour of the combination arm (RR=0.67, 95% CI 0.48 to 0.94). The addition of trastuzumab did not increase the incidence of neutropenia, neutropenic fever or cardiac adverse events.[68, level I] Quality assessment was not mentioned in the study.

Positive outcomes with the addition of trastuzumab to NACT prompted further study on dual anti-HER2 blockade in this setting with the addition of pertuzumab to trastuzumab and chemotherapy. Pertuzumab is a humanised monoclonal antibody directed at the dimerisation domain of HER2. Trastuzumab and pertuzumab have complementary mechanisms of action due to their different binding sites. In the phase II Neosphere trial on women with locally advanced, inflammatory, or early HER2-positive breast cancer, the combination of chemotherapy plus dual anti-HER2 therapy induced a pCR of 45.8% (95% CI 36.1 to 55.7) compared with 29% for trastuzumab + docetaxel, 24% for pertuzumab + docetaxel and 16.8% for dual HER2-blockade without any systemic chemotherapy.[69, level I]

In a phase II TRYPHAENA trial, a study which had cardiac safety as its primary endpoint and a three-arm randomisation, preoperative treatment with pertuzumab and trastuzumab given along with anthracycline-containing (concurrent or sequential) or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer showed pCR rates in all treatment arms ranging from 57% to 66%. The mean change in left ventricular ejection fraction was similar in all treatment arms.[70, level I]

NICE mentions that under National Health Service, 75% of neoadjuvant therapy regimens for patients with HER2-positive cancers contain trastuzumab. NICE also recommends pertuzumab, in combination with trastuzumab and chemotherapy, as an option for neoadjuvant therapy of patients with locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.[25]

NCCN recommends chemotherapy and trastuzumab-based treatment for patients with HER2-positive breast cancer who are candidates for pre-operative systemic therapy. As for dual HER-2 blockade, a pertuzumab containing regimen may be administered pre-operatively to high risk patients i.e. ≥T2 or ≥N1 early stage breast cancer.[26]

Recommendation 18

- Chemotherapy and trastuzumab-based treatment should be offered to patients with HER2-positive breast cancer who require neoadjuvant therapy.

- Addition of pertuzumab as dual HER2 blockade may be considered in high risk patients*.

*Refer to the preceding text.

- **Subcutaneous trastuzumab**

In a large multicentre RCT, the effectiveness and overall safety profile of subcutaneous (SC) trastuzumab were non-inferior to intravenous (IV) formulation in both neoadjuvant and adjuvant setting in patients with HER2-positive, clinical stage I-III breast cancer. Pathological complete response was achieved by 42.2% (95% CI 36.5 to 48.0) of patients in SC group vs 37.4% (95% CI 31.9 to 43.1) in those of IV group with the difference between groups of 4·7% (95% CI -4·0 to 13·4). The adverse event of any grade was comparable between the two groups.[71, level I]

- SC trastuzumab is an alternative to IV trastuzumab in both neoadjuvant and adjuvant setting in patients with HER2-positive, clinical stage I-III breast cancer.

6.3.2 Adjuvant therapy

Adjuvant therapy is used after surgery to reduce the rate of cancer recurrence. It may include chemotherapy, endocrine therapy, targeted therapy or RT.

St. Gallen international consensus panel of experts developed a series of guidelines and recommendations for selection of adjuvant systemic therapy for breast cancer patients based on risk categories (refer to **Table 4**). These are widely used by many oncologists and adapted in various CPG worldwide, including the previous edition of Malaysian CPG on Management of Breast Cancer.

Table 4. Risk categories of breast cancer for adjuvant systemic therapy

Low risk	Intermediate risk	High risk
pN0 and all of the following criteria: • size of tumour maximum 2 cm • Grade 1 • no vessel invasion • ER/PR+ • HER2-negative • age ≥35 years old	pN0 and at least 1 further criterion: • size of tumour >2 cm • Grade 2/3 • vessel invasion • HER2 overexpression • age <35 years old • pN+ (N1 - 3) and HER2-negative	pN+ (N1 - 3) and HER2 overexpression or pN+ (N≥4)

Source: Persing, Monika & Grosse, Regina. (2007). Current St. Gallen Recommendations on Primary Therapy of Early Breast Cancer*. Breast Care. 2. 137-140

a. Chemotherapy

Adjuvant chemotherapy has an established role in eradicating micrometastasis, thus improving survival.[4] Generally, adjuvant chemotherapy is recommended for intermediate or high risk patients. In assessing absolute benefit of systemic adjuvant therapy, NICE recommends the use of PREDICT tool, an online calculator, that is available from the UK NHS website. However, in local setting, a validation study of the tool concludes that while the tool is generally accurate, it needs to be used with caution in patients who are <40 years old and those who have received neoadjuvant chemotherapy.[72]

Taxane-based chemotherapy are incorporated into the management of early and locally advanced breast cancer. Three meta-analyses addressed the effectiveness and safety of taxanes.

In the first meta-analysis, taxane-based regimen improved DFS (OR=0.82, 95% CI 0.76 to 0.88) and OS (OR=0.83, 95% CI 0.75 to 0.91) compared with non-taxane-based regimen in non-MBC. There were no significant differences in the indirect comparison between docetaxel and paclitaxel. However, with nodal positive patients, docetaxel showed greater benefit than paclitaxel in OS (OR=0.79, 95% CI 0.63 to 0.98). The best method of administering paclitaxel was weekly and for docetaxel tri-weekly.[73, level I]

In another meta-analysis, sequential scheduling taxane-anthracycline showed advantages in both DFS (RR=0.90, 95% CI 0.84 to 0.98) and OS (RR=0.88 95% CI 0.79 to 0.98) compared with concurrent scheduling regimen in early breast cancer.[74, level I]

In terms of safety, taxane-anthracycline regimen reduced the incidence of leukaemia (RR=0.40, 95 % CI 0.18 to 0.90), venous thrombosis (RR=0.49, 95 % CI 0.29 to 0.84) and severe cardiac toxicity (RR=0.41, 95% CI 0.26 to 0.66) compared with anthracycline-based regimen in early breast cancer. However, this combination showed higher incidence of neurotoxicity (RR=5.97, 95% CI 1.72 to 20.65) and non-recurrent death (RR=1.79, 95% CI 1.06 to 3.04).[75, level I]

There was no mention on quality assessment in the three meta-analyses.

Recommendation 19

- Taxane-based adjuvant chemotherapy should be offered in patients requiring adjuvant chemotherapy especially in node positive breast cancer.

b. Endocrine therapy

Five years of adjuvant endocrine therapy is the standard of care for hormone receptor-positive breast cancer. The risk of disease recurrence extends well beyond five years after diagnosis and several trials have been performed in recent decade to look into the benefit of extending endocrine therapy beyond the initial five years.

In an RCT, 10 years of tamoxifen reduced the risk of recurrence compared with the standard five years use (RR=0.84, 95% CI 0.76 to 0.94). The breast cancer mortality was also reduced (RR=0.97, 95% CI 0.79 to 1.18) and continued further after reaching 10 years of treatment (RR=0.71, 95% CI 0.58 to 0.88). Cumulative risk of endometrial cancer was 3.1% in extended treatment group and 1.6% in standard treatment group (RR=1.74, 95% CI 1.30 to 2.34).[76, level I]

In a landmark RCT, the addition of letrozole for five years following five years of tamoxifen treatment improved DFS (HR=0.57, 95% CI 0.43 to 0.75), but there was no OS benefit (HR=0.76, 95% CI 0.48 to 1.21). However, hot flushes, arthralgia and arthritis were the most significant side effects with the extended combination treatment.[77, level I]

Extended AI treatment for additional five years following initial five years of AI treatment does not show better DFS (HR=0.85, 95% CI 0.73 to 0.999) or OS (HR=1.15, 95% CI 0.92 to 1.44).[78, level I]

- Current options for adjuvant endocrine therapy in hormone receptor-positive breast cancer include:
  - tamoxifen alone for five years
  - AIs alone for five years
  - sequential treatment with tamoxifen and AIs for five years
  - tamoxifen up to 10 years
  - tamoxifen followed by extended AIs for 10 years

Recommendation 20

- Adjuvant extended endocrine therapy may be offered to hormone receptor-positive breast cancer.

- **Monitoring risk of osteoporotic fracture and management of bone health in patients on aromatase inhibitors**

AIs are commonly used in post-menopausal breast cancer patients. However, their use is associated with risk of fracture due to bone loss.[79]

Risk of fracture can be predicted by measuring patient's bone mineral density using dual-energy X-ray absorptiometry (DEXA) scan. NICE and NCCN recommend all patients on AI to have DEXA scan done

at baseline and periodically thereafter.[25; 26] NICE also recommend bisphosphonates to be started if DEXA scan shows osteoporosis or moderate to severe osteopenia (T score of < -2.0) or an accelerated rate of bone loss (≥4% per year).[25]

An international expert group consensus suggests bisphosphonate should also be started in those with any of the two risk factors of osteoporosis:[80, level III]

- age >65 years old
- T score < -1.5 on DEXA scan
- smoking (current and previous)
- family history of hip fracture
- personal history of fragility fracture above the age of 50 years old
- oral corticosteroids use of >6 months

There are many different types of bisphosphonates or denosumab that can be used in reducing bone loss in patients on AI. However, none of the international guidelines state preference of one agent over the other in term of effectiveness.

Recommendation 21

- All breast cancer patients who are on aromatase inhibitors should have bone densitometry done at baseline and periodically thereafter.
  - Bisphosphonates or denosumab should be started if T score is < -2.0 on dual-energy X-ray absorptiometry or patient has two or more risk factors of osteoporosis*.

*Refer to the preceding text.

c. Ovarian suppression/ablation

For pre-menopausal women, ovarian function can be permanently suppressed by ovarian ablation, accomplished by surgical oophorectomy or ovarian irradiation. Ovarian suppression on the other hand induces temporary amenorrhea by utilising luteinising hormone-releasing hormone agonists. This results in suppression of luteinising hormone and release of follicle stimulating hormone from the pituitary leading to reduced ovarian oestrogen production.

In pre-menopausal patients with high risk early breast cancer of luminal types (ER and/or PR positive) who also received adjuvant chemotherapy, adding ovarian suppression with gonadotropin-releasing hormone agonists (GnRH) to tamoxifen improved DFS and OS compared with tamoxifen alone as evident from the joint analysis of the SOFT and TEXT trials.[81, level I]

In a meta-analysis of 29 RCTs which also included the landmark SOFT study, subgroup analysis showed that ovarian ablation or suppression (OAS) improved DFS and OS in pre-menopausal women aged 40 years or younger with HR of 0.84 (95% CI 0.73 to 0.97) and 0.78 (95% CI 0.66 to 0.94) respectively.[82, level I]

Recommendation 22
- Ovarian ablation or suppression may be offered in premenopausal women with high risk early or advanced stage breast cancer disease.

d. Anti-HER2 therapy

Trastuzumab is recommended in women with HER2-positive breast cancer having adjuvant chemotherapy.[4]

This is supported by a Cochrane systematic review of moderate quality primary papers which showed that adjuvant trastuzumab improved both OS (HR=0.66, 95% CI 0.57 to 0.77) and DFS (HR=0.60, 95% CI 0.50 to 0.71) in early and locally advanced HER2-positive breast cancer patients.[83, level I]

The standard duration of trastuzumab for adjuvant therapy of HER2-positive breast cancer is one year. FinHer study, which evaluated a shorter nine weeks duration of adjuvant trastuzumab in combination with chemotherapy vs without trastuzumab, found improvement in DFS for patients assigned to trastuzumab (HR=0.29, 95% CI 0.13 to 0.64) and generated interest in the de-escalation of adjuvant trastuzumab treatment.[84, level I]

PERSEPHONE, a recent RCT comparing 12 months vs 6 months of trastuzumab in 4,000 women with HER2-positive early breast cancer showed non-inferiority of shorter duration of trastuzumab in 4-year DFS (HR=1.07, 90% CI 0.93 to 1.24, non-inferiority of p=0.011) and 4-year OS (HR=1.14, 90% CI 0.95 to 1.37, non-inferiority of p=0·0010).[85, level I]

However, a meta-analysis of five RCTs including PERSEPHONE trial, showed that one year of trastuzumab was more effective than shorter duration [HR for DFS of 1.31 (95% CI 1.08 to 1.59) and OS of 1.31 (95% CI 1.08 to 1.59)] in HER2-positive breast cancer patients. However, there was no significant difference in DFS in those with node negative disease and hormone positive tumours.[86, level I]

Aphinity trial reported a small improvement in invasive DFS (HR=0.81, 95% CI 0.66 to 1.00) with addition of pertuzumab to trastuzumab treatment in adjuvant setting. However, there was no significant OS benefit (HR=0.89, 95% CI 0.66 to 1.21).[87, level I]

Recommendation 23
- Trastuzumab should be given to women with HER2-positive breast cancer having adjuvant chemotherapy.

- Trastuzumab for six months in adjuvant setting may be considered based on the discretion of the treating clinicians.

6.3.3 Systemic therapy for metastatic disease

Treatment choice in MBC is influenced by many factors:
- patient's factors (age, co-morbidities, performance status, patient's preference and menopausal status)
- tumour biology (hormone receptor and HER2 status)
- previous therapies including toxicities
- disease-free interval
- tumour load/disease burden
- visceral crisis (defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid progression of disease)[63]
- resource availability

Available systemic therapy in MBC:
- endocrine therapy, with or without the addition of a novel agent e.g. cyclin-dependent kinase (CDK) 4/6 inhibitor, mammalian target of rapamycin (mTOR) inhibitor or selective estrogen receptor degrader (SERD), in patients with hormone receptor-positive and HER2 non-amplified MBC
- chemotherapy in patients with rapid clinical progression, life-threatening visceral metastases or need for rapid symptom and/or disease control
- anti-HER2 agent in patient with HER2-amplified disease

a. Chemotherapy

Combination chemotherapy had been shown to be effective first-line treatment in MBC:
- A Cochrane systematic review showed that combination chemotherapy regimens were superior in OS compared with single agent (HR=0.82, 95% CI 0.75 to 0.89) in newly diagnosed or recurrent MBC. The combination regimens were also associated with better time to progression (HR=0.78, 95% CI 0.74 to 0.82) and overall tumour response (RR=1.29, 95% CI 1.14 to 1.45). However, there were more detrimental effect on white cell count, increased alopecia and, nausea and vomiting.[88, level I]
- A later meta-analysis showed similar findings even in MBC patients who have received anthracycline and taxane in adjuvant setting based on OS (HR=0.90, 95% CI 0.84 to 0.96), PFS (HR=0.81,

95% CI 0.76 to 0.88) and overall response rate (RR=1.72, 95% CI 1.34 to 2.21).[89, level I]

- In the absence of medical contraindications or patient concerns, anthracycline or taxane-based regimens are usually considered as first-line chemotherapy for HER2-negative MBC provided there is no prior exposure to anthracycline.[63]

Recommendation 24

- Combination chemotherapy may be considered in fit metastatic breast cancer patients with impending visceral crisis or when rapid resolution of symptoms is required.

b. Endocrine therapy

Endocrine therapy is the preferred option for hormone receptor-positive MBC, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.

- Primary endocrine resistance is defined as relapse while on the first two years of adjuvant endocrine therapy or progression of disease within first six month of first-line endocrine therapy for advanced breast cancer while on endocrine therapy.[63]
- Secondary endocrine resistance is defined as relapse while on endocrine therapy but after the first two years or relapse within 12 months of completing adjuvant endocrine therapy or progression of disease more than six months after initiating endocrine therapy for advanced breast cancer while on endocrine therapy.[63]

The choice of endocrine therapy depends on menopausal status, denovo or relapse presentation at diagnosis of MBC, the type and duration of the therapy in the adjuvant setting as well as the interval between the end of adjuvant ET and the onset of metastatic disease. Endocrine therapy can be used as monotherapy or in combination with a novel agent. The options of monotherapy in MBC include:

- selective estrogen receptor modulator (tamoxifen)
- third generation AIs (anastrazole, letrozole, exemestane)
- SERD (fulvestrant)

The FALCON study showed an improvement in PFS in the fulvestrant group vs anastrazole group (HR=0.797, 95% CI 0.637 to 0.999) as a first-line treatment in hormone receptor-positive, HER2-negative MBC. Higher proportion of arthralgia was also reported in the fulvestrant group.[90, level I]

The options of combination treatment include the pairing of an endocrine agent with:

- CDK 4/6 inhibitor
- mTOR inhibitor

A significant improvement in PFS is seen in the combination treatment of CDK 4/6 inhibitor and an endocrine partner. This benefit is seen in both the pre- and post-menopausal population as stated below.

The Palbociclib: Ongoing Trials in the Management of Breast Cancer-2 (PALOMA-2) study showed that the median PFS was 24.8 months in the palbociclib-letrozole group vs 14.5 months in the placebo-letrozole group (HR=0.58, 95% CI 0.46 to 0.72).[91, level I] These findings were consistent with another Mammary Oncology Assessment of LEE011's 55Efficacy and Safety-2 (MONALEESA-2) trial which showed median PFS of 25.3 months in the ribociclib-letrozole group vs 16.0 months in the placebo-letrozole group (HR=0.568, 95% CI 0.457 to 0.704).[92, level I]

MONALEESA-7 trial demonstrated PFS prolongation extended to pre-menopausal women with the combination of ribociclib and an endocrine partner (tamoxifen, letrozole or anastrazole) and goserelin (HR=0.55, 95% CI 0.44 to 0.69).[93, level I] An updated analysis showed an OS benefit in the ribociclib arm (HR for death=0.71, 95% CI 0.54 to 0.95).[94, level I]

The most common side effect encountered with the combination treatment was neutropenia. Prolonged QTcF interval was also noted in patients in the ribociclib-letrozole arm.[91 - 92, level I]

Another CDK4/6 inhibitor i.e. abemaciclib had been shown to be effective and safe.[95, level I]

- Endocrine therapy in combination with CDK4/6 inhibitor has shown promising results in pre- and post-menopausal, endocrine-naïve hormone receptor-positive, HER2-negative MBC.

In post-menopausal MBC patients who had failed on anastrazole or letrozole, the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study showed an improvement in PFS with the use of everolimus and exemestance compared with exemestane alone (HR for progression or death=0.43, 95% CI 0.35 to 0.54). Higher incidence of serious adverse events were also observed in the combination group including stomatitis and pneumonitis.[96, level I]

Recommendation 25
- Endocrine therapy should be considered as first-line treatment in hormone-receptor positive, HER2-negative metastatic breast cancer unless there is evidence of visceral crisis or endocrine resistance.

c. Anti-HER2 therapy

Therapies that target HER2 have become important agents in the treatment of MBC. A Cochrane systematic review showed that trastuzumab in women with HER2-positive MBC improved both OS (HR=0.82, 95% CI 0.71 to 0.94) and PFS (HR=0.61, 95% CI 0.54 to 0.70). However, the treatment increased the risk of cardiac toxicities e.g. congestive heart failure (RR=3.49, 90% CI 1.88 to 6.47) and left ventricular ejection fraction decline (RR=2.65, 90% CI 1.48 to 4.74).[97, level I]

Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA), a double-blind RCT, compared the effectiveness and safety of pertuzumab in combination with trastuzumab and docetaxel vs trastuzumab and docetaxel as first-line treatment for HER2-positive MBC. It showed improvement favouring the dual HER2-blockade regimen. The median PFS was prolonged by 6.3 months (HR for progression or death=0.68, 95% CI 0.58 to 0.80) and median OS by 15.7 months (HR=0.68, 95% CI 0.56 to 0.84). The addition of pertuzumab did not increase cardiac toxicity. This study also included 10% of patient who had received trastuzumab in the adjuvant setting but with a treatment-free interval of at least six months or longer.[98, level I]

In patients who relapse during adjuvant trastuzumab within six months of completing adjuvant trastuzumab treatment, EMILIA trial showed that trastuzumab emtansine resulted in improved PFS (HR for progression or death=0.65, 95% CI 0.55 to 0.77) and increased median OS (30.9 months vs 25.1 months; HR=0.68, 95% CI, 0.55 to 0.85) compared with lapatinib plus capecitabine. The safety profile was better with the trastuzumab emtansine arm.[99, level I]

Recommendation 26
- Anti-HER2 blockade, may be considered in HER2-positive metastatic breast cancer.

6.3.4 Supportive Therapy

- **Bone-modifying agents in adjuvant and metastatic breast cancer**

Treatment targeting osteoclast activity is important for breast cancer with bone metastases to prevent SREs. Bisphosphonates have been used for this purpose.

A meta-analysis demonstrated that bisphosphonates compared with placebo in adjuvant setting for early breast cancer showed no effect on OS (HR=0.89, 95% CI 0.79 to 1.01) but lower rate of bone fractures (RR=0.59, 95% CI.0.42 to 0.83). Nevertheless, there was a higher rate of osteonecrosis of the jaw/ONJ (RR=7.53, 95% CI 2.91 to 19.50) and pyrexia (RR=3.36, 95% CI 2.61 to 4.32).[100, level I] There was no mention on quality assessment of primary papers in the meta-analysis.

In a recent Cochrane systematic review, bisphosphonates were more effective and safer compared with placebo in adjuvant and MBC. There was a reduction in bone metastases in early breast cancer (RR=0.86, 95% CI 0.75 to 0.99) but not in advanced breast cancer without bone metastases (RR=0.96, 95% CI 0.65 to 1.43). There was also a reduction in risk of SRE (RR=0.86, 95% CI 0.78 to 0.95) in breast cancer with bone metastases. Toxicity was generally mild with rate of ONJ at less than 0.5%.[101, level I]

In a local economic evaluation on different bone modifying agents in MBC, 12-weekly IV zoledranic acid was most cost-effective compared with both denosumab or 4-weekly IV zoledranic acid.[102, level I]

- There is insufficient evidence to recommend the use of adjuvant bisphosphonate in early breast cancer.

Recommendation 27
- Bisphosphanates may be offered in breast cancer patients with bone metastases to reduce skeletal-related events.
  - The preferred regimen is 12-weekly intravenous zoledronic acid.

6.4 Radiotherapy

6.4.1 Radiotherapy post-breast conserving surgery

Adjuvant radiotherapy following BCS reduces risk of local recurrence in the affected breast by half and risk of death by a sixth.[103, level I] All patients with invasive breast cancer who have BCS with clear margin should be offered adjuvant whole breast irradiation (WBI).[4; 25]

Partial breast irradiation (PBI) for early breast cancer is thought to result in comparable local control and better cosmesis. However, a Cochrane systematic review showed that PBI in early stage breast cancer gave worse local control (HR=1.62, 95% CI 1.11 to 2.35) and cosmesis outcome (OR=1.51, 95% CI 1.17 to 1.95) compared with WBI.[104, level I] The finding is supported by another meta-analysis that showed higher local recurrence rate at five years (HR=2.33, 95% CI 1.45 to 3.74) and seven years (HR=1.91, 95% CI 1.30 to 2.79) in PBI compared with WBI.[105, level I]

A later RCT however showed that PBI with intensity modulated radiotherapy (IMRT) technique was non-inferior to those who had WBI in early breast cancer. Late adverse events were similar except for less change in breast appearance (p=0.007) and breast hardening (p<0.0001) in partial breast IMRT.[106, level I]

Intraoperative radiotherapy (IORT) is an alternative option to deliver radiotherapy for early breast cancer. Radiotherapy is delivered during surgery with theoretical advantage of more accurate dose delivery to target. Furthermore, radiotherapy will be delivered only once during surgery compared to the conventional radiotherapy that requires at least 15 times radiation over a course of three to five weeks.[107, level III] However, a meta-analysis showed that IORT yielded higher local recurrence compared with WBI in early stage breast cancer (RR=4.11, 95% CI 0.99 to 17.13).[108, level I]

There is not enough evidence to recommend PBI or IORT as standard of care.[26] NICE considers PBI with IMRT technique only in breast cancer patients who fulfill stringent criteria of low absolute risk of local recurrence.[25]

- IORT may be considered in selected early breast cancer within the scope of clinical trial.
- Partial breast irradiation using intensity modulated radiotherapy may be considered in early stage breast cancer.

Recommendation 28
- Patients with invasive breast cancer who have breast conserving surgery with clear margin should be offered adjuvant radiotherapy

6.4.2 Radiotherapy post-mastectomy

Adjuvant radiotherapy should be offered to the following post-mastectomy patients with ≥4 lymph nodes and positive margin.[4; 25]

However, a recent update of EBCTCG meta-analysis showed that radiotherapy following mastectomy also benefited those with one to three positive lymph nodes:[109, level I]
- LRR (2p<0.00001)
- overall recurrence (RR=0.68, 95% CI 0.57 to 0.82)
- breast cancer mortality (RR=0.80, 95% CI 0.67 to 0.95)

NICE also recommends adjuvant radiotherapy to be considered in node negative but T3 or T4 disease.[25]

Recommendation 29

- Adjuvant radiotherapy should be offered to the following post-mastectomy breast cancer patients with:
  - one or more positive lymph nodes
  - positive margin not amenable for surgery
- Adjuvant radiotherapy should be considered in node negative T3 or T4 breast cancer.

7. FERTILITY PRESERVATION

All oncologic healthcare providers should discuss infertility as a potential risk of treatment when cancer diagnosis is made. Patients who express an interest in fertility and those who are ambivalent or uncertain should be referred to fertility specialist as soon as possible.[110, level II-2; 111] The 'gold standard' for fertility preservation (FP) are embryo and oocytes cryopreservation.[111] Both techniques involve controlled ovarian hyperstimulation (COH) with gonadotropins and will take about 2 - 4 weeks to complete. The mature oocytes retrieved will either be fertilised or cryopreserved for utilisation later.

A large multicentre retrospective cohort study showed non-significance difference in pregnancy outcome between FP for elective reason (EFP) and oncology reason (onco-FP).[112, level II-2]

There has been concern regarding elevated oestrogen levels which may be harmful for patients who are ER+. In a retrospective cohort study, fertility preservation with or without hormonal stimulation had not been shown to increase the rate of breast cancer recurrence.[113, level II-2] In a recent systematic review on safety of COH, the combination of letrozole and gonadotropins during COH reduced oestrogen levels without significant reduction in number of oocytes retrieved.[114, level I]

Ovarian stimulation is not associated with any delay in treatment for breast cancer. It can be started at any point of the menstrual cycle without any decrease in oocyte yield and fertilisation rate.[115, level III]

GnRHa during chemotherapy can be used as an option to preserve ovarian function and fertility in pre-menopausal patients. A meta-analysis showed that premature ovarian insufficiency was lower in patients who had GnRHa during chemotherapy compared with those who did not (OR=0.38, 95% CI 0.26 to 0.57).[116, level I]

- Breast cancer patients who fulfill all the following criteria should be referred for fertility preservation:[110, level II-2; 117]
  - interested in fertility preservation
  - aged <40 years old
  - have good prognosis
  - able to undergo ovarian stimulation and egg collection
  - have enough time to undergo ovarian stimulation before the start of their cancer treatment

Recommendation 30

- Fertility preservation should be discussed with all breast cancer patients in the reproductive age group and suitable patients should be referred to fertility specialist.*
  - Patients' religious belief should be taken into consideration.

*Refer to yellow box above.

8. FAMILIAL BREAST CANCER

Identifying individuals and relatives with inherited predisposition to breast and other cancers has important clinical implications in improving long-term health, including enabling preventive and risk reducing strategies, early detection and increasingly, in treatment options that are targeted towards carriers.

Over the past 10 years, advances in molecular genetics and therapeutics have greatly influenced the practice of genetic counselling and testing for familial breast and ovarian cancers, particularly in three key areas:

i. cost of genetic testing has markedly reduced making it more accessible
ii. identification of other genes associated with inherited susceptibility to breast and/or ovarian cancer has led to multi-gene panel testing, beyond just the BRCA genes
iii. treatment-focussed genetic testing is becoming increasingly important and this has expanded the utility of genetic testing to more than just screening and risk-management and, expanded genetic testing beyond germline to somatic tumour testing

8.1 Cancer Genetic Risk Assessment

For patients concerned about or suspected of having hereditary breast and/or ovarian cancers, initial risk evaluation by the doctor responsible for their care (surgeon or oncologist) should be performed in order to determine if formal risk assessment in a cancer genetics clinic should be undertaken. This initial risk evaluation includes a thorough evaluation of:

i. personal history (including medical and surgical history, patient's needs and concerns)
ii. family history (first- and second-degree relatives on both the maternal and paternal sides) of breast, ovarian and other cancers

Patients should be advised that:

- risk of being a carrier increases with increasing number of affected relatives, the closeness of the relationship and the age at which the affected relative was diagnosed
- maternal and paternal family history should be considered independently
- risk assessment is a dynamic process and can change if additional relatives are diagnosed with cancer

- **Genetic Referral and Testing Guidelines**

NCCN provides comprehensive guidelines on recommended criteria for genetic testing for hereditary breast and ovarian cancer (refer to **Appendix 8**).[118] However, if this broad criteria is applied to all breast

cancer patients in Malaysia, a substantial number of breast cancer patients would need formal risk assessment and counselling, which is neither practical nor cost-effective in today's healthcare service. As such, efforts to simplify and streamline criteria for identifying at-risk individuals for testing while maintaining similar variant detection rate may be necessary. An example that may be used has been evaluated in a Malaysian breast cancer cohort and yielded an approximately 10% mutation detection rate (refer to **Table 5**).[119, level III]

Table 5. Mainstreaming cancer genetics cancer-based criteria

1. Ovarian cancer (epithelial non-mucinous ovarian cancer)
2. Breast cancer in patient diagnosed ≤45 years old
3. Two primary breast cancers, both diagnosed ≤60 years old
4. Triple-negative breast cancer, diagnosed ≤60 years old
5. Male breast cancer
6. Breast cancer plus parent, sibling or child with any of the above criteria

Adapted: Kemp Z, Turnbull A, Yost S, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients with Breast Cancer. JAMA Netw Open. 2019;2(5):e194428

In more well-resourced settings, a number of risk assessment tools have been built to more accurately provide the likelihood of an individual's risk of developing cancer (e.g. Tyrer-Cuzick or BOADICEA risk prediction models) and ongoing efforts to calibrate these for the Asian population are expected to be reported by 2020. Another important upcoming focus is the development of polygenic risk scores for Asian and South-East Asian populations, to improve risk stratification and identify women at higher-risk of breast cancer in these regions. Reference to the latest literature is advised.

8.2 Genetic Counselling and Genetic Testing

For individuals meeting established criteria for one or more hereditary cancer syndromes, genetic testing should be considered along with appropriate pre-test counselling. Such counselling can be provided by a genetic counsellor, medical geneticist, oncologist, surgeon, oncology nurse or other healthcare professional with expertise and experience in cancer genetics. Regardless of who provides the counselling, pre- and post-test counselling should include discussion on the test indications, limitations, potential benefits, possible outcomes and implications.

Genetic testing aims to detect variants in cancer predisposition genes. Previously, single-gene tests were performed, but advances in molecular genetics using parallel testing has enabled the testing of multiple genes simultaneously (multi-gene panel testing). Testing must be comprehensive (including full sequencing and large genomic

rearrangements), for clinically actionable genes and usually offered to an affected family member first. Should a clinically relevant variant be found, testing may then be offered to other adult at-risk relatives.

Individuals eligible for genetic testing may be referred during initial management or at any time thereafter.[5] Rapid genetic counselling and testing (RGCT) may be offered based on individual case needs, after discussion with the genetics team. An RCT reported that female breast cancer patients who received RGCT and subsequently received DNA test results before surgery were more likely to undergo direct bilateral mastectomy compared with women who received the usual care (OR=3.09, 95% CI 1.15 to 8.31).[120, level I] NICE recommends fast-track genetic testing (within four weeks of diagnosis of breast cancer) only as part of a clinical trial.[5]

8.3 Genetic Predisposition to Breast Cancer

Understanding of genetic predisposition to breast cancer has advanced beyond BRCA1 and BRCA2, with numerous genes in which variants confer a moderate risk (2 - 4-fold higher risk) or high risk (>4 times higher risk) of breast cancer compared with the general population.[121] Refer table below for genes and associated risk of breast cancer.

Table 6. Genes for which breast cancer risk has been established

Gene	Estimated Relative Risk (90%CI)	Absolute Risk by 80 Years of Age (%)	Other Associated Cancers
BRCA1	11.4	75	Ovary
BRCA2	11.7	76	Ovary, prostate, pancreas
TP53	105 (62 to 165)		Childhood sarcoma, adrenocortical carcinoma, brain tumours
PTEN	No reliable estimate		Thyroid, endometrial cancer
CDH1	6.6 (2.2 to 19.9)	53	Diffuse gastric cancer
STK11	No reliable estimate		Colon, pancreas, ovarian sex cord-stromal tumours
PALB2	5.5 (3.0 to 9.4)	45	Pancreas
CHEK2	3.0 (2.6 to 3.5)	29	Lung, although p.Ile157Thr is associated with reduced risk
ATM	2.8 (2.2 to 3.7)	27	Pancreas
NF1	2.6 (2.1 to 3.2)	26	Malignant tumours of peripheral nerve sheath, brain, central nervous system
NBN	2.7 (1.9 to 3.7)	23	Unknown

Adapted: Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243-57

The genes BARD1, RAD51C and RAD51D are associated with an increased risk to breast cancer, but risk estimates remain inaccurate because these variants are rare. With more upcoming evidence, the increasing importance of these genes is anticipated and reference to latest literature is encouraged to obtain more accurate risk estimates in this rapidly evolving area.

8.4 Clinical Management for Carriers of Pathogenic/Likely Pathogenic Variants in BRCA1, BRCA2 and Other Genes

BRCA1 and BRCA2 are highly penetrant genes and pathogenic/likely pathogenic variants are associated with early-onset breast cancers and increased risk of contralateral breast cancer, ovarian cancer, prostate and pancreatic cancer (BRCA2 only).[122]

- Individuals with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 have an increased risk of breast, ovarian and a number of related cancers. Hence these individuals warrant consideration of earlier and more intensive screening and preventive strategies.

Post-test counselling in individuals with pathogenic/likely pathogenic variants in BRCA1 or BRCA2 should include screening, risk-reducing surgeries and chemoprevention. A multidisciplinary approach and shared decision making should be practised in all risk management strategies.

In the last 10 years, carriers of variants in PALB2, ATM and CHEK2 genes have also been associated with increased risk to breast cancer, but clinical evidence on screening and risk-reducing surgery remains lacking. Other complicated, rare syndrome genes including TP53, PTEN, CDH1 and STK11 are usually best managed in consultation with a clinical genetics team that is outside the scope of this CPG.

Individuals with strong family history of cancer but with no pathogenic/likely pathogenic variants or whom do not undergo genetic testing, may benefit from further risk assessment using calibrated tools, such as BOADICEA, and offered screening according to their estimated lifetime risk of cancers. The CanRisk tool is a web interface to BOADICEA and can be accessed at https://canrisk.org/about/

8.4.1 Intensive screening

Intensive screening for breast cancer in BRCA carriers and high risk individuals starts considerably earlier than standard recommendations.[123] Breast awareness education with monthly breast self-examination should begin at 18 years of age and biannual CBE should begin at 25 years of age.[118] Other screening strategies, based on age and risk group are summarised in the table below.

Table 7. Summary of recommendations on screening for women with no personal history of breast cancer

Age (years)	Average risk of breast cancer[1]	Moderate risk of breast cancer[2]	High risk of breast cancer (but with a 30% or lower probability of being a BRCA or TP53 carrier)[3]	Known BRCA1 or BRCA2 carrier
20 - 29	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI
30 - 39	Do not offer mammography	Do not offer mammography	Consider annual mammography	Annual MRI and consider annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	
40 - 49	Do not offer mammography	Annual mammography	Annual mammography	Annual mammography and annual MRI
	Do not offer MRI	Do not offer MRI	Do not offer MRI	
50 - 59	Mammography as part of population screening	Consider annual mammography	Annual mammography	Annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast
60 - 69	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening	Annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast
70+	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening

[1]Lifetime risk of developing breast cancer is <17%.
[2]Lifetime risk of developing breast cancer is at least 17% but <30%. This is likely to include individuals with pathogenic/likely pathogenic variants in PALB2 regardless of family history of breast cancer and, individuals with pathogenic/likely pathogenic variants in ATM and CHEK2 and at least one first

degree relative affected by breast cancer. Individuals with pathogenic/likely pathogenic variants in ATM or CHEK2 and no close family history of breast cancer is considered to be of low/moderate risk of breast cancer (i.e. <17% lifetime risk).

[3]Lifetime risk of developing breast cancer is at least 30%. This is likely to include individuals with pathogenic/likely pathogenic variants in PALB2 and strong family history of breast cancer, or individuals where BOADICEA or other risk prediction tools suggest a high risk based on family history of breast cancer.

Adapted: National Institute for Health and Clinical Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. London: NICE; 2018

Recommendation 31
- Intensive screening of BRCA carriers and high risk individuals should be vigilantly performed and adhered to recommended guidelines.
- Screening of women with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 should be conducted from age 30 to 49 years with both magnetic resonance imaging and mammography. Those 50 years and above, screening with mammography should be done.

8.4.2 Risk-reducing strategies

i) Risk-reducing surgery

- **Bilateral risk-reducing mastectomy**

Risk-reducing mastectomy (RRM) remains the most effective strategy for reducing breast cancer risk. A meta-analysis showed that prophylactic bilateral mastectomy reduced the risk for breast cancer (RR=0.11, 95% CI 0.04 to 0.32) but not all-cause mortality.[124, level II-2] Another systematic review also showed 90 - 95% risk reduction.[125, level II-2]

Multidisciplinary consultations are recommended prior to surgery and should include discussions of the risks and benefits of surgery and option of breast reconstruction. Psychosocial effects of RRM should also be addressed.

For carriers of pathogenic/likely pathogenic variants of PALB2, ATM and CHEK2, there is currently insufficient evidence for RRM and these individuals are managed based on family history.[25]

- **Contralateral risk-reducing mastectomy**

Carriers of pathogenic/likely pathogenic variants of BRCA1 and BRCA2 have increased risk of developing contralateral breast cancer. A prospective study showed average cumulative risks by age 70 years of 83% (95% CI 69 to 94) for BRCA1 and 62% (95% CI 44 to 79.5) for BRCA 2.[126, level II-2] BRCA 1 particularly has higher risks as the majority of tumours would not receive endocrine therapy.[127, level III] Further risk factors for contralateral breast cancer within BRCA carriers include early age of first breast cancer diagnosis (<50 years) with increasing numbers of first-degree relatives with breast cancer at a young age.[127, level III; 128, level II-2]

Contralateral risk-reducing mastectomy reduces risk of contralateral breast cancer by over 90% in BRCA1 and BRCA2 carriers[129, level II-2] and is associated with 48 - 63% survival advantage.[129 - 130, level II-2]

For carriers of pathogenic/likely pathogenic variants of PALB2, ATM and CHEK2, there is currently insufficient evidence for increased risk to contralateral breast cancer.

- **Risk-reducing bilateral salpingo-oophorectomy**

Risk-reducing bilateral salpingo-oophorectomy (RRSO) remains the most effective risk reduction strategy for the prevention of BRCA1- and BRCA2-associated ovarian, fallopian tube and peritonial cancers. A Cochrane systematic review of moderate quality primary papers showed RRSO reduced risk of gynaecological cancers in both BRCA1 and BRCA2.[131, level II-2]

Pre-menopausal high risk women are most likely to benefit from RRSO, but also most likely to experience side effects from surgery, including loss of fertility, loss of sexual function and increased osteoporosis. Thus, RRSO is advised after completion of childbearing and from the age of 35 - 40 years old.

Notably, whereas earlier meta-analyses suggested that RRSO may reduce the risk of breast cancer, two recent studies presented strong evidence suggesting that the previous reports may have been subject to ascertainment bias. Correction for this bias suggested that RRSO provided no or minimal protective effect on breast cancer risk.[132 - 133, level II-2]

Recommendation 32

- Risk-reducing surgeries should be discussed and offered to women with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 genes.

ii) Chemoprevention

- **Selective estrogen receptor modulators**

A long-term RCT on tamoxifen as chemoprevention (20 mg for five years) for moderate and high risk women (as determined using the Tyrer Cuzick Model) found a reduction in the occurrence of all breast cancers in the tamoxifen group compared with placebo group (HR=0.71, 95% CI 0.60 to 0.83). After 20 years of follow-up, the estimated risk of developing all types of breast cancer was 12.3% (95% CI 10.1 to 14.5) in the placebo group compared with 7.8% (95% CI 6.9 to 9.0) in the tamoxifen group; hence the NNT for five years to prevent one breast cancer in the next 20 years was 22 (95% CI 19 to 26).[134, level I]

A higher incidence of deep vein thrombosis in women receiving tamoxifen compared with placebo was seen in the first 10 years of follow-up (OR=1.87, 95% CI 1.11 to 3.18). Although not significant, there were more endometrial cancers in the tamoxifen group, but only for the first five years of active treatment.[134, level I]

Women on tamoxifen should stop tamoxifen two months before trying to conceive or six weeks before elective surgery.[5]

- **Aromatase inhibitors**

In an RCT of anastrozole as chemoprevention in post-menopausal high risk women (as determined using the Tyrer Cuzick Model), after a median follow-up of five years, fewer women in the anastrozole group developed breast cancer compared with placebo group (HR=0.47, 95% CI 0.32 to 0.68). The predicted cumulative incidence of all breast cancers after seven years was 5.6% in the placebo group and 2.8% in the anastrozole group, suggesting that 36 women (95% CI 33 to 44) would need to be treated with anastrozole to prevent one cancer in seven years of follow-up.[135, level I]

Anastrozole was not associated with an increased risk of other cancers particularly gynaecological cancers, nor any thromboembolic or vascular events. A contraindication for anastrozole use was severe osteoporosis.[135, level I]

- **Oral contraceptives**

For female carriers of pathogenic/likely pathogenic variants in BRCA1 or BRCA2, use of oral contraceptive could reduce the risk of ovarian cancer, with no significant increase in risk to breast cancer.[118]

- In high risk women, evidence has shown that risk-reducing surgeries and chemoprevention are effective in reducing the risk of developing breast cancers.

8.4.3 Role of poly (ADP-ribose) polymerase inhibitors for BRCA carriers

Poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib or talazaparib) can be considered as a treatment option for patients with BRCA-associated advanced triple negative breast cancer or luminal metastatic breast cancer, after failure of chemotherapy and endocrine therapy. Its use is associated with a PFS benefit, improvement in quality of life and a favourable toxicity profile.[63]

9. FOLLOW-UP

Regular follow-up visits are recommended every 3 - 4 months in the first two years, every 6 - 8 months from subsequent years 3 - 5 and annually thereafter. The interval of visits should be adapted to the risk of relapse and patients' needs. The recommended surveillance are.[136]

- annual ipsilateral (after BCS) and/or a contralateral mammography (after mastectomy), with US and breast MRI when needed
- regular bone density evaluation for patients on AIs or undergoing ovarian function suppression
- encouragement towards adopting a healthy lifestyle, including diet modification and exercise

Approximately 5% of breast cancer patients will have a risk to develop a new ipsilateral or contralateral cancer and it persists over time. There is limited evidence on surveillance strategies in older breast cancer survivors. The American Cancer Society has recommended screening mammography should be continued beyond 75 years old as long as a woman is in good health and is expected to live 10 more years or longer.[137] Nevertheless, current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older.[138]

10. SUPPORTIVE TREATMENT

- This chapter is written mainly based mainly on the previous edition of CPG Management of Breast Cancer (Second Edition) and not on new clinical questions. The CPG DG opines that for complete management of breast cancer, the supportive treatment is summarised and mentioned here. Some updates are done on Psychosocial Assessment and Intervention Section.

a. Psychosocial assessment and intervention

Most breast cancer patients experience at least some psychosocial distress during the course of their diagnosis and treatment. A local study revealed that up to 47.1% of women with breast cancer experience psychological distress, depression (25.3%), anxiety (18.8%)[139] and post-traumatic stress disorder (19.6%).[140]

Other common psychosocial concerns reported by women with breast cancer include:[141]

- fear of recurrence
- physical symptoms e.g. fatigue, sleep disturbance or pain
- body image disruption
- sexual dysfunction
- treatment-related anxieties
- intrusive thoughts about illness/persistent anxiety
- marital/partner communication
- feelings of vulnerability
- existential concerns regarding mortality

Local studies showed that psychosocial issues impact patients' overall well-being. In the currently challenging global economic state, almost half of Malaysian families with cancer survivors experienced financial constraints.[142] Other related issues include lack of constant psychosocial support and proclivity of undesirable consequences e.g. delaying treatment and/or not turning up for treatment at all.[143; 144; 145; 146; 147; 148; 149; 150]

Women with breast cancer should be screened for emotional distress using validated self-assessment psychological tests by trained healthcare providers.[4] Psychological distress for them should be assessed at key time points throughout the cancer trajectory. This should be done at diagnosis, during and after completion of treatment throughout the survivorship period. Recommended screening tools for this purpose include Patient Health Questionnaire (PHQ) and Emotion Thermometer (ET). While the Hospital Anxiety and Depression Scale was previously widely used, it is now copyrighted and requires payment to use.

The aim of a psychological intervention is to reduce emotional and mental burden as well as to equip patients with accurate information and psychological skills to manage their distress. The following psychosocial interventions should be offered by trained healthcare providers particularly for women with emotionally vulnerability following a diagnosis of breast cancer:[4]

- cognitive behaviour therapy
- psychosocial support
- psycho-education programmes (e.g. printed materials, audio-visual materials, telephone support and counselling)

Others include Managing Cancer and Living Meaningfully,[151; 152] Mindfulness Therapy,[153] and Acceptance and Commitment Therapy.[154]

b. Breast care nurse

Breast care nurse (BCN) improves the continuity of care and provide important information, support and referral for a wide range of needs experienced by breast cancer patients. All patients should have access to a BCN for treatment of breast cancer. Improving BCN accessibility includes:[155]

- clarification on the role focusing on psychosocial assessment and support of the patients
- appropriate training, accreditation and ongoing professional development
- inclusion in MDT
- availability in rural and remote areas through telephone and video conferencing calls
- funding for positions should be ongoing and sustainable

A breast care nurse (BCN) should be assigned to all patients to provide information on management and psychosocial support throughout the diagnosis, treatment and follow-up.[4]

c. Lifestyle modifications

Lifestyle changes can be recommended to patients as an adjunct to standard breast cancer treatment.[156]

The Malaysian breast cancer cohort study showed that there was a high proportion of breast cancer survivors being obese and overweight.[148; 157] Breast cancer survivors should have balance diet and maintain lean body mass. There is still no particular style of diet that has been found to be more beneficial for reducing the risk of breast cancer recurrence.[156]

Healthy lifestyle is associated with a lower risk of recurrence and this should include:

- achieving and maintaining a healthy weight through regular physical activity and dietary modification; regular physical activity

(at least 150 minutes/week) has the most robust effect of all lifestyle factors on reducing breast cancer recurrence[156]
- limiting alcohol intake to below five units per week (3 or 4 alcoholic drinks per week or 6 g of alcohol per day)[25]
- smoking cessation[25]

d. Palliative care

Palliative care aims to improve quality of life of patients and their families in facing the life-threatening illness by effective pain management and other distressing symptoms. It also incorporates psychosocial and spiritual care according to patient/family needs, values, beliefs and cultures.[158] Palliative care is the main focus of care when cure is not achievable.[26]

Palliative care begins at diagnosis of advanced breast cancer. It should be delivered concurrently with disease-directed therapies and facilitate patient's autonomy on the further management based on the medical information.

- Palliative care should be initiated by the primary care team and then augmented by a palliative care physician.

Essential components of palliative care include the following:[26]
- establishment of rapport and relationships with patients and family/ caregivers
- management of symptoms, psychosocial/spiritual distress and functional status
- exploration of patients' understanding and education about illness and prognosis
- clarification of treatment goals
- assessment and support of coping needs
- assistance with medical decision making
- coordination with other care providers
- provision of referrals to other care providers as indicated

e. Patient Navigation Programme

Patient navigation programme (PNP) is a community-based service delivery intervention designed to promote access to timely diagnosis and treatment of cancer and other chronic diseases by eliminating barriers to care.[159, level III]

Principles of PNP are:
1. Navigation is a patient-centric healthcare service delivery model.
2. The core function of navigation is the elimination of barriers to timely care across all levels of healthcare which is most effectively carried out through a one-on-one relationship between the navigator and the patient.

3. Patient navigation should be defined to distinguish the role and responsibilities of the navigator from that of all other providers. Navigators should be integrated into the healthcare team in order to achieve maximum benefit for the individual patient.
4. Delivery of navigation services should be cost-effective and commensurate with the training and skills necessary to navigate an individual through a particular phase of the care.
5. The determination of whom should navigate should be primarily decided by the level of skills required at a given phase of navigation ranging from trained lay investigators to professional providers.
6. There is a need to define the point where navigation begins and ends; the need is not over until the cancer is resolved.
7. There is a need to navigate patients across disconnected level of care i.e. from primary to tertiary care.
8. Navigation systems require coordination. In larger systems of patient care, the coordination is best carried out by assigning a navigation coordinator or champion who is responsible for overseeing all phases of navigation activity within a given healthcare level.

PNP has the potential to reduce cancer-related disparities and improve outcomes by eliminating barriers to obtain quality cancer care. PNP in cancer care is effective in improving screening rates, adherence to follow-up following an abnormal results and timeliness of diagnosis.[159, level III] Minimal research has indicated that PNP is effective for post-treatment surveillance.[160, level I]

Malaysia is one of the countries with lower relative survival rate in the Asia-Pacific, with only 66.8% of patients having 5-year survival rate, mainly due to late presentation and poor adherence to evidence-based treatment.[2, level II-2]

Studies in psychosocial factors show that fear, poor health education and lack of empowerment among Malaysians are major reasons causing delay and defaulting treatment. In order to address these challenges, Cancer Research Malaysia identifies the PNP as a potential community-based solution to improve the Malaysian survivorship of breast cancer.[161]

f. Breast cancer patient support groups

Breast cancer patient support groups are invaluable resources for support, services and information which include:

- provision of emotional, social and material support for individuals with breast cancer
- empowering breast cancer patients to self-care during and after treatment
- public education on breast cancer awareness

Breast cancer patient support groups play a crucial role in making patients adapted with their disease. A case-control study showed that patients supported by a peer group enjoyed a higher quality of life compared with others.[162, level II-2] Locally, the breast cancer support groups are such as:

- Breast Cancer Welfare Association Malaysia
- Pink Unity (National Cancer Society Malaysia)
- Breast Cancer Foundation (formerly known as Pride Foundation)
- Pink Ribbon
- KanWork

- The following additional management is important and should be considered for breast cancer patients when indicated:
  - psychosocial assessment and intervention
  - breast care nurse
  - lifestyle modifications
  - palliative care
  - patient navigation programme
  - breast cancer patient support groups

Refer to **Appendix 9** on **Post-Treatment Cancer Survivorship (Management of Treatment Complications)**

11. IMPLEMENTING THE GUIDELINES

The management of breast cancer should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

11.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

a. wide dissemination of the CPG to healthcare providers (hard- and soft-copies)
b. regular topic update for healthcare providers via continuous medical education (seminar/conference/course)
c. National Cancer Registry
d. National Key Performance Indicator i.e. margin on BCS
e. involvement of non-governmental organisations e.g. breast cancer support groups in Breast Cancer Awareness Month

Existing barriers for application are:

a. lack of understanding/limited knowledge on breast cancer
b. insufficient resources including expertise, diagnostic tools, medications, equipment
c. variation in clinical management and preferences

11.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:

a. ensure widespread distribution of CPG & its implementation strategies
b. strengthen training to ensure up-to-date information being shared
c. provide adequate resources in the management of breast cancer
d. provide multidisciplinary team at different levels of care
e. strengthen the cancer registry
f. empower community with active involvement in disease-related activities

The following is proposed as clinical audit indicator for quality management of breast cancer:

$$\text{Percentage of patients with suspected breast cancer* referred within two weeks to the breast clinic**} = \frac{\text{Number of patients with suspected breast cancer referred within two weeks to the breast clinic in a period}}{\text{Number of patients with suspected breast cancer in the same period}} \times 100\%$$

*Women aged >35 years with signs and symptoms, high risk group with signs and symptoms and patients with clinical signs of malignancy
**Target of 80%

$$\text{Percentage of breast cancer patients with clear surgical margins in BCS***} = \frac{\text{Number of breast cancer patients with clear surgical margins in BCS in a period}}{\text{Number of breast cancer patients with BCS in a period}} \times 100\%$$

***Target of 85%

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What is the adequate tumour free margin in breast conserving surgery in breast cancer?

1. BREAST NEOPLASMS/
2. (breast adj1 (cancer or carcinoma* or neoplasm* or tumo*)).tw.
3. (breast malignant adj2 (neoplasm* or tumo*)).tw.
4. (human mammary adj2 (cancer or carcinoma* or neoplasm* or tumo*)).tw.
5. cancer of breast.tw.
6. cancer of the breast.tw.
7. malignant neoplasm of breast.tw.
8. malignant tumo?r of breast.tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. MASTECTOMY, SEGMENTAL/
11. breast quadrantectom*.tw.
12. breast conserv* adj2 therap*.tw.
13. ((breast conserv* or breast-conserv* or breast sparing or breast-sparing) adj2 surger*).tw.
14. lumpectom*.tw.
15. ((partial or segmental) adj1 mastectom*).tw.
16. segmentectom*.tw.
17. wide local excision.tw.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18
20. tum?r margin.tw.
21. 19 and 20
22. limit 21 to (english language and humans and yr=”2010 -Current”)

Appendix 2

CLINICAL QUESTIONS

A. Risk factors
- What are the risk factors for breast cancer?

B. Screening
- What are the effective screening methods of breast cancer in:
  - general population?
  - high risk group?

C. Referral
- What are the criteria for referral to surgical or breast clinic?

D. Assessment/Diagnosis
- What are the effective approaches for imaging-histopathology discordance in breast lesions?
- What is the accuracy of tomosynthesis in the diagnosis of breast cancer?
- What is the accuracy of imaging-guided biopsy in breast lesions?
- What are the elements of adequate imaging report for breast cancer?
- What is the accuracy of Ki-67 as a predictor and prognostic marker in breast cancer?
- What is the accuracy of HER2 test in core biopsy specimen of breast cancer?

E. Staging
- Is positron emission tomography (PET) or PET/computed tomography accurate and effective in the staging of breast cancer?

F. Treatment (based on stage)
- What is the role of multidisciplinary team in breast cancer?
- What is the adequate tumour free margin in breast conserving surgery in breast cancer?
- Is neoadjuvant systemic therapy effective and safe for breast conserving surgery in breast cancer?
- What is the effective and safe subsequent treatment after sentinel lymph node biopsy in early breast cancer?
- Is surgery of primary tumour effective and safe in metastatic breast cancer?
- When is the optimal timing for breast reconstruction (with or without prosthesis) in breast cancer requiring post-operative radiotherapy?
- What is the most effective and safe taxane-based regimen in early breast cancer?
- Is anti-HER2 treatment effective and safe in neoadjuvant, adjuvant and metastatic breast cancer?
- Is subcutaneous transtuzumab effective and safe in breast cancer?

- Is ovarian suppression/ovarian ablation effective and safe in pre-menopausal breast cancer?
- Is endocrine therapy effective and safe in breast cancer?
- Is intraoperative radiotherapy/partial breast irradiation effective and safe in breast cancer?
- What is the effective and safe first-line systemic therapy in metastatic breast cancer?
- How to monitor the risk of osteoporotic fractures in patients with breast cancer on aromatase inhibitors?
- Are bone-modifying agents effective and safe in adjuvant and metastatic breast cancer?
- Which group of breast cancer patients need to be referred for fertility preservation?
- What are the effective and safe interventions for fertility preservation in breast cancer?
- What is the effective and safe local treatment of metastatic breast cancer?
- What is the effective and safe treatment in loco-regional recurrent breast cancer?

G. Survivorship Programme

- When to stop surveillance mammography in breast cancer?

H. Familial Breast Cancer

- Who should be offered genetic counselling and testing for inherited risk to hereditary breast and ovarian cancer? When is the optimal timing to do it?
- What are the effective clinical management strategies for those with inherited risk of hereditary breast and ovarian cancer?
- What are the effective clinical management strategies in BRCA carriers?

Appendix 3

RECOMMENDED REPORTING SYSTEM

INTRODUCTION

The ACR BI-RADS Atlas 2013 (4) is the updated version of the 2003 Atlas. BI-RADS® is designed to standardise breast imaging reporting and to reduce confusion in breast imaging interpretations. It also facilitates outcome monitoring and quality assessment.

It contains a lexicon for standardised terminology (descriptors) for mammography, breast US and MRI, as well as chapters on Report Organisation and Guidance for use in daily practice.

A. REPORT ORGANISATION

A good reporting system should be concise and organised using the following structure.

THE STANDARD REPORTING SYSTEM:

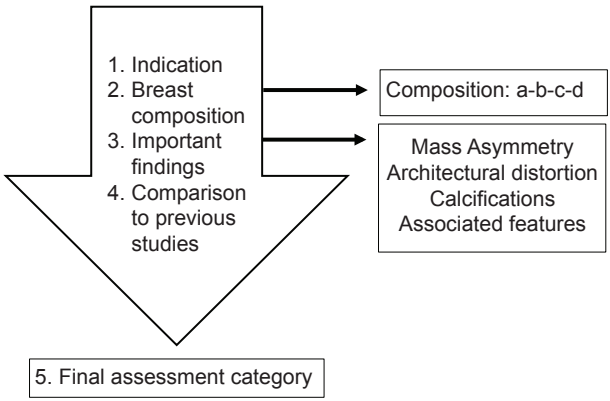
A statement indicating that the current examination has been compared to previous examination(s) should be included (specify date[s]). If this is not included, it should be assumed that no comparison has been made, although it is preferable to indicate that no comparison was made.

Below are the components of standard reporting system:

1. *Describe the indication for the study.*
2. *Describe the breast composition.*
3. *Describe any significant finding using standardised terminology.*
4. *Compare to previous studies.*
5. *Conclude to a final assessment category.*

   Use BI-RADS categories 0 - 6 and the phrase associated with them. If mammography and US are performed: overall assessment should be based on the most abnormal of the two breasts, based on the highest likelihood of malignancy.
6. *Give management recommendations.*
7. *Communicate unexpected findings with the referring clinician.*

Standard Reporting



6. Give recommendations on management
7. Communicate unsuspected findings with the referring clinician

1. Describe the indication for the study

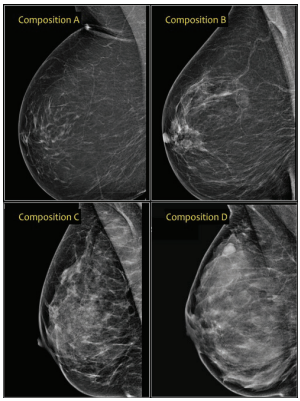
The examination is for screening, diagnostic or follow-up. Mention patient's history.

If US is performed, mention if it is targeted to a specific location or supplementary screening. If an implant is present, both standard and implant-displaced views should be performed and, this should be stated in the mammography report.

2. Describe the breast composition

In the BI-RADS 2003 edition, the assignment of the breast composition was based on the overall density resulting in ACR category 1 (<25% fibroglandular tissue), category 2 (25 - 50%), category 3 (50 - 75%) and category 4 (>75%).

In BI-RADS 2013, the use of percentages is discouraged because in individual cases, it is more important to take into account the chance that a mass can be obscured by fibroglandular tissue than the percentage of breast density as an indicator for breast cancer risk.



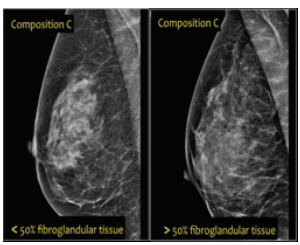
In the BI-RADS edition 2013, the assignment of the breast composition is changed into a, b, c and d-categories followed by a description:

a- *The breasts are almost entirely fatty.*
Mammography is highly sensitive in this setting.

b- *There are scattered areas of fibroglandular density.*
The term density describes the degree of x-ray attenuation of breast tissue but not discrete mammographic findings.

c- *The breasts are heterogeneously dense, which may obscure small masses.*
Some areas in the breasts are sufficiently dense to obscure small masses.

d- *The breasts are extremely dense, which lowers the sensitivity of mammography.*



Notice in the left example, the composition is c - heterogeneously dense, although the volume of fibroglandular tissue is less than 50%.
The fibroglandular tissue in the upper part is sufficiently dense to obscure small masses.
So, it is called c, because small masses can be obscured.
Historically this would have been called an ACR 2: 25 - 50% density.
The example on the right has more than 50% glandular tissue and is also called composition c.

3. Describe any significant finding using standardized terminology

Use the morphological descriptors: mass, asymmetry, architectural distortion and calcifications.

These findings may have associated features, like for instance a mass can be accompanied with skin thickening, nipple retraction, calcifications, etc.

Correlate these findings with the clinical information, mammography, US or MRI.

Integrate mammography and US findings in a single report.

a. Mass:

Size
Morphology (shape, margin)
Density
Associated calcifications
Associated features
Location

b. Calcifications:

Morphology - describe typically benign or malignant type by describing the shape of particles
Distribution
Associated features

c. Architectural Distortion:
Associated calcifications
Associated features
Location
d. Asymmetries (asymmetry, global asymmetry, focal asymmetry, developing asymmetry):
Associated calcifications
Associated features
Location
e. Intramammary lymph node (rarely important):
Location
f. Skin lesion (rarely important):
Location
g. Solitary dilated duct (rarely present):
Location

Mammography and US Lexicon

The table below shows a summary of the mammography and US lexicon.
Enlarge the table by clicking on the image.
First describe the breast composition.
When there is a significant finding, use the descriptors in the table.
The US lexicon has many similarities to the mammography lexicon, but there are some descriptors that are specific for US.

<table>
<tr><th colspan="4">Mammography Lexicon</th><th colspan="3">Ultrasound Lexicon</th></tr>
<tr><td>Breast composition</td><td colspan="3">A. entirely fatty
B. scattered areas of fibroglandular density
C. heterogeneously dense, which may obscure masses
D. extremely dense, which lowers sensitivity</td><td>Breast composition</td><td colspan="2">a. homogenous - fat
b. homogenous - fibroglandular
c. heterogenous</td></tr>
<tr><td rowspan="3">Mass</td><td>shape</td><td colspan="2">oval - round - irregular</td><td rowspan="5">Mass</td><td>shape</td><td>oval - round - irregular</td></tr>
<tr><td>margin</td><td colspan="2">circumscribed - onscured - microlobulated - indistinct - spiculated</td><td>margin</td><td>circumscribed or not circumscribed:
indistinct, angular, microlobulated, spiculated</td></tr>
<tr><td>density</td><td colspan="2">fat - low - equal - high</td><td>orienta-tion</td><td>parallel - not parallel</td></tr>
<tr><td>Asymmetry</td><td colspan="3">asymmetry - global - focal - developing</td><td>echo pattern</td><td>anechoic - hyperechoic - complex cyctic/solid hypoechoic - isoechoic - heterogenous</td></tr>
<tr><td>Architectural distortion</td><td colspan="3">distorted parenchyma with no visible mass</td><td>posterior features</td><td>no features - enhancement - shadowing - combined pattern</td></tr>
<tr><td rowspan="3">Calcifications</td><td>morpho-logy</td><td colspan="2">typically benign</td><td>Calcifications</td><td colspan="2">in mass - outside mass - intraductal</td></tr>
<tr><td></td><td>suspi-cious</td><td>1. amorphous
2. coarse heterogenous
3. fine pleiomorphic
4. fine linear or fine linear branching</td><td>Associated features</td><td colspan="2">architectural distortion - duct changes - skin thickening - skin retraction - edema - vascularity (absent, internal, rim) - elasticity</td></tr>
<tr><td>distribu-tion</td><td colspan="2">diffuse - regional - grouped - linear - segmental</td><td rowspan="2">Special cases (cases with a unique diagnosis)</td><td colspan="2" rowspan="2">simple cyst - clustered microcysts - complicated cyst - mass in or on skin - foreign body (including implants) - intramammary lymph node - AVM - Mondor disease - postsurgical fluid collection - fat necrosis</td></tr>
<tr><td>Associated features</td><td colspan="3">skin retraction - nipple retraction - skin thickening - trabecular thickening - axillary adenopathy - architectural distortion - calcifications</td></tr>
</table>

US-Breast Imaging Lexicon
Many descriptors for US are the same as for mammography. For instance when describe the shape or margin of a mass.

Below are findings that are specific for US:
Breast composition:
- Homogeneous echotexture-fat
- Homogeneous echotexture-fibroglandular
- Heterogeneous echotexture

Mass:
- Orientation: unique to US-imaging, and defined as parallel (benign) or not parallel (suspicious finding) to the skin.
- Echo pattern: anechoic, hypoechoic, complex cystic and solid, isoechoic, hyperechoic, heterogeneous.
  Echogenicity can contribute to the assessment of a lesion, together with other feature categories. Alone it has little specificity.
- Posterior features: enhancement, shadowing.
  Posterior features represent the attenuation characteristics of a mass with respect to its acoustic transmission, also of additional value. Alone it has little specificity.

Calcifications:
- On US poorly characterised compared with mammography, but can be recognised as echogenic foci, particularly when in a mass.

Special cases - cases with a unique diagnosis or pathognomonic US appearance:
- Simple cyst
- Complicated cyst
- Clustered microcysts
- Mass in or on skin
- Foreign body including implants
- Lymp nodes - intramammary
- Lymph nodes- axillary
- Vascular abnormalities
- Post-surgical fluid collection
- Fat necrosis

Correlate these findings with clinical information or findings of mammography, US or MRI. Intregrate the mammography and US findings in a single report.

4. Comparison to previous examination(s), if deemed appropriate by the interpreting physician

Awaiting to compare with previous examination may assume importance if the finding of concern requires an evaluation of change or stability. Comparison is not important when a finding has unequivocally benign features. Comparison may be irrelevant when the finding is inherently suspicious for malignancy.

5. Conclude to final assessment category

The BI-RADS® assessment categories are designed to be concordant with specific management recommendations. The linking of assessment categories with concordant management recommendations further enhances sound medical practice.

If mammography and US are performed; the overall assessment should be based on the most abnormal of the two breasts, based on the highest likelihood of a malignancy.

An incomplete (category 0) assessment is usually given for screening examinations when additional imaging evaluation is recommended before it is appropriate to render a final assessment.

In category 0 assessment should include specific suggestions for the next course of action (spot-compression magnification views, US etc)

Final Assessment Categories			
Category		**Management**	**Likelihood of Cancer**
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	Not applicable
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably benign	Short interval follow-up (six months) or continued surveillance	>0% but ≤2%
4	Suspicious	Tissue diagnosis	4a. low suspicion of malignancy (>2% to ≤10%) 4b. moderate suspicion of malignancy (>10% to ≤50%) 4c. high suspicion of malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	Not applicable

6. Give management recommendations.

7. Communicate unexpected findings with referring clinician.

The verbal discussions between radiologist, patient and referring clinician should be documented in the clinical notes/report.

Adapted: Radiology Assistant (Available at: https://radiologyassistant.nl/breast/bi-rads-for-mammography-and-ultrasound-2013)

Appendix 4

BREAST IMAGING SURVEY FORM

JABATAN RADIOLOGI

Hospital _____

Tel: _____ Ext: _____ / _____ or NGCS_____

BREAST IMAGING SURVEY FORM (Please fill in into two copies)

RN: _____ IC/Passport No: _____

Name: _____

Request: ☐ Screening ☐ Diagnostic ☐ Additional Views

Previous imaging & date: _____

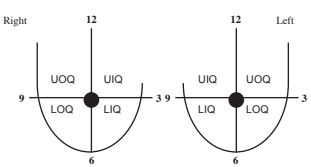
Menarche ☐ y/o Menarche ☐ y/o LMP ☐☐ ☐☐ / ☐☐☐☐
Day Month Year

Parity ☐ Number of children ☐ Breastfed (in months) ☐☐

Risk Factors	Remarks
Family History of Cancer (Relationship & age of onset)	
Personal History of Cancer (Breast, Ovarian and others)	
Hormonal history (HRT/OCP and others)	
Genetic testing (BRCA 1, BRCA 2 and others)	

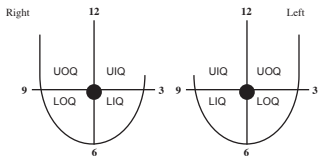
Clinical Data	Right		Left		Remarks
	Yes	No	Yes	No	
Breast pain/tenderness					
Lump in breast					
Nipple discharge					
Skin & nipple charges					
Nipple retraction/Inversion					
Axillary nodes swelling					
Biopsy history & HPE					
Previous surgical intervention (Surgery/Implant/RT/ChemoTx)					

Impression:



_____
Signature & stamp of the Medical Officer/Specialist

RADIOGRAPHER FINDINGS:-



Please note any:

Scar	
Mole	
Lump	
Nipple changes	
Skin Folds	

Projection		**kVp**	**mAs**	**Thickness**	**Dose**	**No. of images**	**PGMI score**
Right	**CC**						
	MILO						
Left	**CC**						
	MILO						
Additional views							
Repeat projections							

BIRADS Breast composition: | **a** | **b** | **c** | **d** | **e** |

Signature of Radiographer)

RADIOLOGIST REPORT:-

Please tick (✓) where appropriate

Findings	**RT**	**LT**
Mass		
Architectural distortion		
Asymmetrical density		
Calcification : (i) **Macro** (ii) **Macro**		
Axillary nodes		
Others		

Impression:

BIRADS Category:- | **0** | **1** | **2** | **3** | **4** | **5** | **6** |

Recommendation:-

Signature & stamp of the Medical Officer/Specialist

Source: Ministry of Health Malaysia. Makluman Penggunaan Borang Permohonan Pemeriksaan Radiologi bagi Perkhidmatan Radiologi Yang Baharu Di Fasiliti Kementerian Kesihatan Malaysia. Putrajaya 6 November 2018

Appendix 5

TNM CLASSIFICATION OF BREAST CANCER

Definition of Primary Tumor (T) – Clinical and Pathological

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor <20 mm in greatest dimension
T1mi	Tumor <1 mm in greatest dimension
T1a	Tumor >1 mm but <5 mm in greatest dimension (round any measurement 1.0-1.9 mm to 2 mm).
T1b	Tumor >5 mm but <10 mm in greatest dimension
T1c	Tumor >10 mm but <20 mm in greatest dimension
T2	Tumor >20 mm but <50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see "Rules for Classification")

*Note: Lobular carcinoma in situ (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cáncer Staging Manual, 8lh Edition.

Definition of Regional Lymph Nodes - Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi"	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level 1, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.

*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

“cN 1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Definition of Regional Lymph Nodes - Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1 - 3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1 - 3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4 - 9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4 - 9 axillary lymph nodes (at least one tumor deposit larger than 2 .0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes.

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
MI	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

*Note that imaging studies are not required to assign the cMO category

AJCC Anatomic Stage Groups

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available. Cancer registries in the U.S. must use the Prognostic Stage Group table for case reporting.

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Source: American Joint Committee on Cancer. AJCC Cancer Staging Manual, Eighth Edition. Springer; 2017

Appendix 6

HISTOPATHOLOGY WORKSHEET FOR BREAST BIOPSY/ MASTECTOMY

HSB/PAT/HIS/BOR/01
(Breast Cancer Pin 1/2015)

KEMENTERIAN KESIHATAN MALAYSIA
PERKHIDMATAN PATOLOGI
HOSPITAL .....

HISTOPATHOLOGY WORKSHEET FOR BREAST BIOPSY/MASTECTOMY

Name:	**HPE No:**
	IC No:

PATHOLOGIST & MO IN-CHARGE: **GROSSING DATE:** **NOTES:**

SLIDES READY ON:

Received by:	*Blocking:	No of blocks:	*Slides to MO:
Grossed by:	*Sectioning:	No of slides:	*Slides to Pathologist:
Assisted by:	*Staining:	*QC check:	*** Please write date and name/initials**

SPECIMEN CONTAINER LABELED AS:

1. GROSS DESCRIPTION

1.1. Type of specimen: ☐ Mastectomy - ☐ Right ☐ Left
☐ Mastectomy with axillary resection - ☐ Right ☐ Left
☐ Re-excision (completion mastectomy) - ☐ Right ☐ Left
☐ Lumpectomy/excision biopsy (weight: ..... grams)
☐ Hookwire Localization biopsy (weight: ..... grams)
☐ Wide excision (weight: ..... grams)

1.2. Size: Breast tissue:
Axillary tissue:
Skin tissue:

1.3. Appearance of skin & nipple:

1.4. Description of lesion(s)
Focality: ☐ Single ☐ Multiple
Site: ☐ UOQ ☐ UIQ ☐ LOQ ☐ LIQ
☐ Central ☐ _____
Size:
Appearance:
Additional comments:

1.5. Distance from tumour to resection margins:

Superior - Medial -
Inferior - Lateral -
Deep - Superficial -

1.6. Number of lymph nodes retrieved: ..... (..... mm to ..... mm in diameter)

1.7. Sampling (see below)
Grossed by:

2. HISTOLOGY

2.1. Microscopic description:
Histological type: ☐ Invasive carcinoma (NST)
☐ Invasive lobular carcinoma
☐ Mucinous carcinoma
☐ Tubular carcinoma
☐ Papillary carcinoma
☐ Medullary
☐ Other:

Tubular score: ☐ 1 ☐ 2 ☐ 3
Nuclear score: ☐ 1 ☐ 2 ☐ 3
Mitoses: ☐ 1 ☐ 2 ☐ 3
Comment:

2.2. Modified Bloom & Richardson grade: ☐ 1 (score: ……/9) ☐ 2 (score: ……/9)
☐ 3 (score: ……/9)

2.3. Tumour size: - Whole tumour (invasive & DCIS) size: ……. mm
- Invasive tumour size: ……. mm

2.4. Tumour extent: ☐ Localised ☐ Multiple invasive foci

2.5. Vascular/lymphatic invasion: ☐ Not seen ☐ Present ☐ Possible

2.6. Pathologic response to neoadjuvant therapy (RCPA Australasia 2012):
☐ Not applicable
☐ No definite response
☐ Partial pathologic response
☐ Complete pathologic response
(Refer explanatory notes):

2.7. Associated lesion(s):
- DCIS: ☐ No
☐ Yes:
- Histologic type: _____
- Nuclear grade: ☐ High ☐ Intermediate ☐ Low
- Necrosis ☐ Absent ☐ Present
- Microcalcification: ☐ No ☐ Yes
- Extensive intraductal component (≥25%): ☐ No ☐ Yes

- LCIS/Lobular neoplasia: ☐ No ☐ Yes
- Other abnormalities: ☐ No ☐ Yes (specify):

2.8. Skin and nipple: - Paget's disease ☐ No ☐ Yes
- Other comments:

2.9. Resection margins (in relation to both invasive and in-situ components):

2.10. Axillary lymph nodes: Total retrieved - ……
Number positive - ……
Extranodal extension: ☐ No ☐ Yes (? no lymph nodes)
If single node positive: ☐ Macrometastasis (>2 mm)
☐ Micrometastasis (0.2 mm to 2 mm)
☐ Isolated tumour cells (<0.2 mm)
Comment on sentinel lymph node (if applicable):

2.11. Immunohistochemical study:
- Oestrogen receptor*: ☐ +ve ☐ -ve (…… % of tumour cells)
- Progesterone receptor*: ☐ +ve ☐ -ve (…… % of tumour cells)
- c-erb B2: ☐ +ve ☐ -ve ☐ Equivocal/weakly positive (2+)

*Staining of ≥1% of cells of any intensity is considered positive (ASCO/CAP Guidelines).
*For microinvasive tumour, please comment on ER/PR status in DCIS component.

☐ Done on previous biopsy: Please refer to HPE report _____

3. FINAL INTERPRETATION

Source: Ministry of Health Malaysia. Jemputan Menghadiri Bengkel 'Standardization of Reporting' Anatomik Patologi, 2015. Kota Bharu 28 Julai 201

MEDICATIONS IN SYSTEMIC THERAPY OF BREAST CANCER AND THEIR COMMON SIDE EFFECTS

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
CHEMOTHERAPY		
Capecitabine	• Cardiotoxicity: uncommon but can be fatal • Gastrointestinal: diarrhoea, nausea, vomiting, mucositis, abdominal pain • Hand-foot syndrome • Liver: Hyperbilirubinemia • General: fatigue/weakness	• Use with caution in patients with history of heart disease • Dose reduction is a must in patients with moderate renal dysfunction • Monitor for hand-foot syndrome
Cyclophosphamide	• Cardiotoxicity: uncommon but can be fatal • Urotoxicity (bladder ulceration, necrosis, fibrosis, contracture): seldom but can be fatal • Haematological: myelosuppression (leukopenia, neutropenia, thrombocytopenia, anaemia) • Gastrointestinal: nausea, vomiting, abdominal discomfort, anorexia, diarrhoea • Dermatological: alopecia, rashes, pigmentation, changes in nails	• Use with caution in patients with history of heart disease • Monitoring of complete blood counts is essential • Used with caution in patients with active urinary tract infection • Advise patient to report urinary symptoms
Docetaxel	• Haematological: neutropenia, anaemia, febrile neutropenia, thrombocytopenia, infections • Dermatological: hypersensitivity, neuropathy, skin reactions, alopecia, nail disorders • Gastrointestinal: dysgeusia (taste disturbance), constipation, anorexia, nausea, vomiting, diarrhoea, mucositis • Respiratory: dyspnoea • General: myalgia, asthenia, pain, fluid retention	• Prophylactic anti-emetic and corticosteroids should be given • Use with caution in patients with history of liver impairment and heart disease • Should not be given to patients with neutrophil counts of <1500 cells/mm^3 • Monitor blood count

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
Doxorubicin	• Cardiovascular: cardiotoxicity, i.e. cardiomyopathy, congestive heart failure (seldom, irreversible and can be fatal) • Dermatological: extravasation, skin necrosis, cellulitis, vesication, local phlebitis, thrombophlebitis, reversible alopecia, erythematous streaking along vein proximal to site of injection, phlebosclerosis • Gastrointestinal: nausea, vomiting, mucositis (stomatitis, oesophagitis), diarrhoea, abdominal pain • Haematological: myelosuppression, leucopenia, haemorrhage • General: dehydration, facial flushing (if an injection has been given too rapidly)	• Use with caution in patients with history of heart disease • Cardiac function should be assessed before undergoing treatment and has to be carefully monitored throughout therapy • Contraindicated in patients with marked liver impairment • Initial treatment requires close observation and extensive laboratory monitoring
Epirubicin	• Cardiac toxicity: seldom, irreversible and can be fatal • Haematological: leukopenia, neutropenia, anaemia, thrombocytopenia • Gynaecological: amenorrhea • Gastrointestinal: nausea, vomiting, mucositis, diarrhoea • Dermatological: keratitis, alopecia, local skin toxicity, rash/itch • Opthalmological: conjunctivitis • General: lethargy, infection	• Use with caution in patients with history of heart disease • Use with caution in patients with hepatic impairment • Cardiac function should be assessed before undergoing treatment and has to be carefully monitored throughout therapy
Eribulin	• Haematological: neutropenia, anaemia • Dermatological: alopecia • Gastrointestinal: nausea, constipation • General: asthenia/fatigue • Peripheral neuropathy	• Monitor complete blood counts prior to each dose; increase frequency of monitoring in patients who develop Grade 3 or 4 cytopenias

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
Fluorouracil (5-FU)	• Gastrointestinal: diarrhoea, stomatitis, oesophagitis, heart burn • Haematological: anaemia, leukopenia, thrombocytopenia • Hand-foot syndrome • Cardiovascular: angina pectoris, myocardial infarction, arrhythmia, acute pulmonary oedema • Dermatological: alopecia, dermatitis	• Prophylactic anti-emetic and corticosteroids should be given • Use with caution in patients with history of heart disease • Monitor hand-foot syndrome
Gemcitabine	• Gastrointestinal: nausea, vomiting • Haematological: neutropenia, anaemia, thrombocytopenia • Hepatological: increased liver enzymes • Nephrological: proteinuria, haematuria • Respiratory: dyspnoea • Dermatological: rash • General; fever, oedema	• Monitor for myelosuppression prior to each cycle • Monitor renal function and hepatic function prior to initiation and during treatment
Paclitaxel	• Haematological: anaemia, infections • Dermatological: hypersensitivity reaction, irritation at injection site, alopecia • Gastrointestinal: nausea, vomiting, diarrhoea, mucositis • Neuropathy • General: myalgia, oedema, hypotension	• Patients should be pretreated with corticosteroids, diphenhydramine and H_2 antagonists • Should not be given to patients with neutrophil counts of <1500 cells/mm^3 • Monitor blood count
Vinorelbine	• Haematological: neutropenia, anaemia • Liver enzyme elevation • Gastrointestinal: nausea, vomiting, constipation • Dermatological: injection site reaction • Peripheral neuropathy • General: asthenia	• Monitor complete blood counts prior to each dose; do not administer to patients with neutrophil counts <1000 cells/mm^3 • Monitor liver function during treatment • Consider routine stool softener during treatment

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
TARGETED THERAPY		
Abemaciclib	• Gastrointestinal: diarrhoea, nausea, vomiting, abdominal pain, decreased appetite • Haematological: neutropenia, leukopenia, thrombocytopenia, anaemia, infections • General: fatigue, headache	• Monitor complete blood counts prior to the start of therapy, every 2 weeks for first 2 months, monthly for the next 2 months and as clinically indicated
Ado-trastuzumab emtansine	• Infusion-related reactions: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia • Gastrointestinal: nausea, constipation • Haematological: thrombocytopenia • Hepatological: increased liver enzymes • Vascular: haemorrhage, epistaxis • Musculoskeletal pain, peripheral neuropathy • General: headache, fatigue, arthralgia	• Hepatotoxicity and cardiac toxicity: uncommon but can be fatal • Use with caution in patient with history of hepatic impairment and heart disease • Evaluate cardiac function prior to and during treatment
Everolimus	• Gastrointestinal: stomatitis, diarrhoea, abdominal pain, nausea, decreased appetite • Haematological: infections, fever, rash • Respiratory: cough • General: fatigue, asthenia, oedema, headache	• Monitor complete blood count prior to starting and every 6 months for the first year of treatment
Lapatinib	• Gastrointestinal: diarrhoea, nausea, vomiting • Hand-foot syndrome • Dermatological: rash • General: fatigue	• Monitor hand-foot syndrome

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
Olaparib	• Gastrointestinal: nausea, vomiting, abdominal pain, diarrhoea, dysgeusia, dyspepsia, decreased appetite, constipation, stomatitis • Haematological: neutropenia, leukopenia, infections • General: fatigue, asthenia, dizziness	• Monitor hematological toxicity at baseline and monthly thereafter
Palbociclib	• Haematological: neutropenia, leukopenia, anaemia, thrombocytopenia, infections • General: fatigue, asthenia, pyrexia • Gastrointestinal: nausea, diarrhoea, vomiting, stomatitis, decreased appetite • Dermatological: alopecia, rash	• Monitor complete blood count prior to start therapy and at the beginning of each cycle, on day 15 of the first 2 cycles and as clinically indicated
Pertuzumab	• Left ventricular dysfunction: seldom but can be fatal • Infusion reactions: pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, nausea, vomiting, rash • Gastrointestinal: diarrhoea • Haematological: neutropenia • General: fatigue	• Evaluate cardiac function prior to and during treatment
Ribociclib	• Haematological: neutropenia, leukopenia, infections • Gastrointestinal: nausea, vomiting, diarrhoea, constipation • Dermatological: alopecia, rash • Respiratory: cough • General: fatigue, headache	• Use with caution in patients with history of heart problems and hepatic impairment • Perform complete blood count before initiating therapy; monitor it every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically indicated
Trastuzumab	• Cardiotoxicity: can be fatal • Infusion reactions: fever, chills, nausea, vomiting, pain (in some cases at tumour sites), headache, dizziness,	• Evaluate cardiac function prior to and during treatment • Prophylactic antihistamines should be given

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
	dyspnoea, hypotension, rash, asthenia • Gastrointestinal: diarrhoea • Haematological: neutropenia, anaemia, infections • Respiratory: cough • General: fatigue, myalgia	
HORMONAL THERAPY		
Anastrozole	• Dermatological: hot flushes, rash • Musculoskeletal: arthritis, pain, back pain, bone pain, arthralgia, asthenia • Hypertension, headache • Depression, insomnia • Gastrointestinal: nausea, vomiting, pharyngitis • Bone: osteoporosis, fractures • Peripheral oedema, lymphoedema • Respiratory: cough, dyspnoea	• Monitor bone mineral density throughout treatment
Exemestane	• Dermatological: hot flushes, sweating • Gastrointestinal: nausea, increased appetite • General: fatigue	• Monitor bone mineral density
Fulvestrant	• Gastrointestinal: nausea, vomiting, constipation, anorexia • Dermatological: injection site pain, hot flushes • Musculoskeletal: bone pain, back pain, musculoskeletal pain, arthralgia, fatigue • Respiratory: dyspnoea • Increased hepatic enzymes	• Use with caution in patients with hepatic impairment
Letrozole	• Dermatological: hot flushes, flushing • Headache, dizziness • Arthralgia, asthenia • Oedema	• Monitor bone mineral density throughout treatment

MEDICATION	COMMON SIDE EFFECTS	COMMENTS
	• Hypercholesterolaemia • Increased sweating • Bone and musculoskeletal pain	
Tamoxifen	• Gastrointestinal disorders: nausea • General disorder: fatigue/asthenia	• Use with caution in patients with history of thromboembolic events

Sources:

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23. Femara® (letrozole) [package insert]. East Hanover, NJ: Novartis, Inc: 2014.
24. Nolvadex®-D (ribociclib) [package insert]. Mississauga, Ontario: AstraZeneca Canada, Inc: 2015.

Appendix 8

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalised risk assessment, genetic counselling and, often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known BRCA1/2 pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 years of age
  - Diagnosed 46 - 50 years of age with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 years of age with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 years of age; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[g] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer or metastatic prostate cancer[g] at any age or breast cancer <50 years of age; or
  - ≥2 close blood relatives[e] with breast or prostate cancer at any age; or
  - Ashkenazi Jewish ancestry[h]

- BRCA1/2 pathogenic/likely pathogenic variant detected by tumour profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood[e] relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

[a] For further details regarding the nuances of genetic counselling and testing, see BR/OV-A.
[b] Irrespective of degree of relatedness
[c] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included
[d] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumours either synchronously or asynchronously
[e] Close blood relatives include first-, second- and third-degree relatives on same side of family (see BR/OV-B)
[f] Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumours. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumours can also be associated with other rare syndromes. Examples include an association between sex-cord tumours with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
[g] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.
[h] Testing for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s), should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations.
[i] Approximately 2 - 5% of unselected cases of pancreatic adenocarcinoma will have BRCA1/2 pathegonic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of BRCA1/2 pathogenic/like pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (see NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, YU J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390.
[j] E.g., PARP inhibitors for ovarian cancer and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer. See the relevant NCCN treatment guidelines (e.g. NCCN Guidelines for Breast Cancer; NCCN Guidelines for Prostate Cancer) for further details.
[k] This may be extended to an affected third-degree relative if related through two male relatives (e.g. paternal grandfather's mother or sister).

Source: National Comprehensive Cancer Network Guidelines Version 3.2019. BRCA-Related Breast and/or Ovarian Cancer Syndrome. NCCN; 2019.

Appendix 9

POST-TREATMENT CANCER SURVIVORSHIP (MANAGEMENT OF TREATMENT COMPLICATIONS)

Breast cancer patients may be at risk of developing treatment-related complications. Thus, healthcare providers must recognise and manage the long-term sequelae of the constellation of therapeutic modalities. There is limited evidence for multidisciplinary rehabilitation among these populations. A systematic review concluded that multidisciplinary rehabilitation was not harmful and may improve functional ability and quality of life in the short-term.[1]

- **Breast cancer-related lymphoedema**

Breast cancer-related lymphoedema (BCRL) is a common consequence of breast cancer treatment. Patient should be counselled on ways to prevent or reduce risk of lymphedema. Weight loss for those who are overweight or obese may reduce this risk.[2,3] Good evidence showed that there was no increased risk of BRCL with exercise; thus patient should not restrict or avoid physical activity.[4] Patients should be routinely examined for clinical symptoms or swelling suggestive of lymphoedema. They should be referred to therapists knowledgeable about the diagnosis and treatment of it.

- Physiotherapist plays an important role in the rehabilitation care of women with breast cancer as well as the care of the survivors.

- **Late onset cardiotoxicity**

Occurrence of late onset cardiotoxicity associated with chemotherapy is generally low except for anthracycline especially if dose given is above the limit. If occur, it typically presents as reduced left ventricular function failure. In contrast, trastuzumab cardiotoxicity usually occur during treatment and does not have risk of delayed cardiotoxicity.[5]

Identification of high-risk patients including patients with pre-existing heart problems, cardiovascular (CV) risk factors and treatments like trastuzumab and anthracyclines,[6] education of patients on healthy lifestyle modifications, aggressive management of underlying CV risk factors, consideration of cardioprotective strategies and, routine surveillance of left ventricular function before and after therapies are recommended to reduce breast cancer treatment-associated cardiotoxicities.[7] Aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardiotoxicity.[5]

- **Cognitive impairment**

Cognitive impairment is one of the frequent complications reported by patients with breast cancer. All patients need to be screened for cognitive impairment and to identify reversible contributing factors e.g. organic brain disease, mood disorder, endocrine problem, dehydration, infections or medication-related and optimally treat when possible.

- **Fatigue**

Studies of long-term cancer survivors suggested that approximately one-quarter to one-third experienced persistent fatigue for up to 10 years after cancer diagnosis.[8] Fatigue has a negative impact on work, social relationship, mood and daily activities. It causes impairment in overall quality of life during and after treatment. All patients should be assessed for fatigue and treated for any causative factors including anaemia, cardiac dysfunction, depression, sleep disturbance, etc. Patients without otherwise identifiable cause are encouraged to engage in regular physical activity and cognitive behavioural therapy as appropriate.

- **Pain**

Approximately 20 - 50% of patients complain of pain during the survivorship period. Types of pain may be nociceptive, neuropathic or mixed pattern.[9,10] Pain will lead to physical, emotional, spiritual and functional discomfort. Pain can be assessed with a comprehensive history taking and simple pain scales e.g. visual analog scale. Aetiology of the pain needs to be identified before initiation of treatment. Refer to CPG on Management of Cancer Pain.[11]

- **Bone health**

Survivors of breast cancer are at high risk of significant bone loss. Assessment of bone mineral density in high risk patients as detailed below are:[12]

  - post-menopausal survivors should have a baseline DEXA scan
  - a repeat DEXA scans every two years should be done for:
    - women taking AIs
    - pre-menopausal women on GnRHa
    - women who have chemotherapy-induced premature menopause

Non-pharmacologic interventions including lifestyle changes, vitamin D and calcium supplements are extremely important.[13]

Source:

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LIST OF ABBREVIATIONS

3D	three-dimensional
^{18}FDG	(^{18}F)-fluorodeoxyglucose
ACR	American College of Radiology
AGREE	Appraisal of Guidelines for Research and Evaluation
AIs	aromatase inhibitors
ALND	axillary lymph nodes dissection
ASR	Age-Standardised Incidence Rate
AUC	area under the curve
BCRL	Breast cancer-related lymphoedema
BCS	breast conserving surgery
BCSS	breast cancer-specific survival
BI-RADS®	Breast Imaging Reporting and Data System
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BR	breast reconstruction
BRCA	BReast CAncer gene
CBE	clinical breast examination
CDK	cyclin-dependent kinase
CI	confidence interval
cm	centimetre
cm^3	centimetre square
COH	controlled ovarian hyperstimulation
CPG(s)	clinical practice guidelines
CT	computed tomography
CV	cardiovascular
DBT	digital breast tomosynthesis
DCIS	ductal carcinoma in situ
DEXA	dual-energy X-ray absorptiometry
DFS	disease free survival
DMFS	distant metastasis-free survival
DOR	diagnostic odds ratio
ER(-/+)	estrogen receptor (negative/positive)
FFDM	full-field digital mammography
FNAC	fine needle aspiration cytology
FP	fertility preservation
g	gramme
GnRHa	Gonadotropin-releasing hormone agonists
IBTR	ipsilateral breast tumour recurrences
IHC	immunohistochemistry
ISH	in-situ hybridisation
IV	intravenous
HER2(-/+)	Human Epidermal Growth Factor Receptor 2 (negative/positive)
HR	hazard ratio
LA	luminal A
LABC	locally advanced breast cancer
LB	luminal B
LCIS	lobular carcinoma-in-situ
LR	local recurrence
LRR	locoregional recurrence
MBC	metastatic breast cancer
MCG	Mainstreaming Cancer Genetics

MDT	multidisciplinary team
MET	metabolic equivalent of task
MIBT	minimally invasive biopsy technique
mg	milligramme
MoH	Ministry of Health
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NACT	neoadjuvant chemotherapy
NET	neoadjuvant endocrine therapy
OAS	ovarian ablation or suppression
OC	oral contraceptives
ONJ	osteonecrosis of the jaw
OR	odds ratio
OS	overall survival
PBI	partial breast irradiation
PET	positron emission tomography
PFS	progression free survival
PMRT	post-mastectomy radiation therapy
PNP	patient navigation programme
PR(-/+)	progesterone receptor (negative/positive)
RCT(s)	randomised controlled trial(s)
RGCT	rapid genetic counselling and testing
RR	relative risk
RS	relative survival
RRM	risk-reducing mastectomy
RRSO	risk-reducing bilateral salpingo-oophorectomy
RT	radiotherapy
SC	subcutaneous
SERD	selective estrogen receptor degrader
SLND	sentinel lymph nodes dissection
SLNs	sentinel lymph nodes
SREs	skeletal-related events
SRS	stereotactic radiosurgery
TE	tissue expander
TNM	Tumour Node Metastasis
US	ultrasound
vs	versus
WBI	whole breast irradiation
WBRT	whole brain radiotherapy
WHO	World Health Organization

ACKNOWLEDGEMENT

The DG members of these guidelines would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Technical Advisory Committee of CPG for their valuable input and feedback
- Health Technology Assessment and Clinical Practice Guidelines Council for approval of the CPG
- Ms. Rosnani Abdul Latip on retrieval of evidence
- Professor Dr. Nur Aishah Mohd. Taib, Dr. Caryn Chan Mei Hsien and Ms. Nur Haidzat Abdul Wahid on Psychological Assessment and Intervention Section
- Assoc. Prof. Dr. Julia Patrick Engkasan, Head & Consultant Rehabilitation Physician, and Dr. Chan Soo Chin, Senior Lecturer & Rehabilitation Physician, Pusat Perubatan Universiti Malaya on Post-Treatment Cancer Survivorship Chapter
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both DG and RC had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. Details are available upon request from the CPG Secretariat.

SOURCE OF FUNDING

The development of the CPG on Management of Breast Cancer (Third Edition) was supported financially in its entirety by the MoH Malaysia.

ISBN 978-967-2173-99-1

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