MANAGEMENT OF BREAST CANCER
(Third Edition)
# Key Messages

1. Breast cancer is the most important cancer among women in Malaysia. Regardless of gender, it contributed to 19.0% of all new cancer cases diagnosed in 2012 - 2016.

2. Nearly half of the breast cancer patients are diagnosed at stage III & IV (47.9%). Thus, increasing awareness is important for early detection.

3. Screening mammography for breast cancer may be performed biennially in women aged 50 - 74 years in the general population. For those with high risk, offer screening from 30 years of age.

4. Patients with symptoms & signs of breast cancer should be referred to breast clinic within 2 weeks.

5. Triple assessment which consists of clinical assessment, imaging [ultrasound (US) and/or mammography] & pathology (histology and/or cytology) is required in breast cancer diagnosis.

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

7. Surgery is the mainstay of treatment for early breast cancer, consists of breast conserving surgery (BCS) or mastectomy with sentinel lymph node (LN) biopsy or axillary dissection.

8. Breast cancer is a systemic disease. Hence, systemic therapy and/or radiotherapy have an established role in eradicating micro-metastasis to improve survival.

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

10. Individuals suspected of having hereditary breast and/or ovarian cancers should have initial risk evaluation in order to determine if formal risk assessment in a cancer genetics clinic should be undertaken.

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This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Breast Cancer (Third Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
- Academy of Medicine Malaysia: [www.acadmed.org.my](http://www.acadmed.org.my)

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RISK FACTORS

• The cause of the vast majority of breast cancers remains unknown. However, established risk factors include:

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
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<tbody>
<tr>
<td>• Increasing age</td>
<td>• Nulliparity</td>
</tr>
<tr>
<td>• Female</td>
<td>• Lack of breastfeeding</td>
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<tr>
<td>• Family history of breast cancer at a young age</td>
<td>• Hormonal factors: oral contraceptives, hormone replacement therapy, unopposed oestrogen use in hysterectomised women, etc.</td>
</tr>
<tr>
<td>• A carrier of pathogenic or likely pathogenic variants in genes e.g. BRCA1, BRCA2, PALB2, ATM &amp; CHEK2</td>
<td>• Lifestyle: overweight, lower level of physical activity, etc.</td>
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<tr>
<td>• Early menarche (≤12 years old) or late menopause (≥50 years old)</td>
<td>• Radiation exposure</td>
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<tr>
<td>• History of neoplastic disease of breast</td>
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<tr>
<td>• Increased mammographic density</td>
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CRITERIA FOR EARLY REFERRAL

• Patients with any of the following conditions should be referred early (within 2 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

ASSESSMENT AND DIAGNOSIS

i. Radiological Reporting

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

Standard Reporting

1. Indication
2. Breast composition
3. Important findings
4. Comparison to previous studies

Composition: a-b-c-d
Mass Asymmetry
Architectural distortion
Calcifications
Associated features

5. Final assessment category
6. Give recommendations on management
7. Communicate unsuspected findings with the referring clinician
SURGICAL MARGIN

SYSTEMIC THERAPY

- Estrogen receptor (ER) & progesterone receptor (PR) 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.
- The staging of breast cancer is based on Tumor Nodes Metastasis (TNM) Classification of The American Joint Committee on Cancer (AJCC)
- Early breast cancer includes cancer of stage I, stage IIA & stage IIB.
- No tumour at ink margin on histopathological examination is adequate for BCS in invasive breast carcinoma.
- In women treated with BCS for ductal carcinoma in situ of <2 mm margin, the benefits & risks of further treatment (surgery or radiotherapy) should be discussed to reduce the risk of local recurrence.

Neoadjuvant Therapy

- Inoperable breast cancer should be referred for neoadjuvant systemic therapy prior to surgical intervention.
- Neoadjuvant chemotherapy may be offered to patients with triple negative or HER2-positive early breast cancer to enable BCS but its benefits & risks need to be discussed with the patients.

Adjuvant Therapy

- Adjuvant therapy should be offered based on assessment of risks & benefits (refer table on risk categories).
- Taxane-based adjuvant chemotherapy should be offered in patients requiring adjuvant chemotherapy especially in node positive breast cancer.
- Adjuvant extended endocrine therapy may be offered to hormone receptor-positive breast cancer.
- Trastuzumab should be given to women with HER2-positive breast cancer having adjuvant chemotherapy.

Final Assessment Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
<th>Likelihood of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Need additional imaging or prior examinations</td>
<td>Recall for additional imaging and/or await prior examinations</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
<td>Routine screening</td>
</tr>
<tr>
<td>2</td>
<td>Benign</td>
<td>Routine screening</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign</td>
<td>Short interval follow-up (6 months) or continued surveillance</td>
</tr>
</tbody>
</table>
| 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 |

ii. Tissue Sampling

- 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.

iii. Histopathological Examination

Adequate surgical pathology reporting of breast cancer using standard proforma with minimum dataset should have:
- maximum diameter of invasive tumour
- location (side & quadrant), multifocality/multicentricity
- tumour type (histology according to WHO classification)
- histological grade
- LN involvement and total number of nodes examined
- resection margins
- lymphovascular invasion
- non-neoplastic breast changes
- hormone receptor status: ER/PR
- HER2/c-erb B2 assessment
• Estrogen receptor (ER) & progesterone receptor (PR) status should be assessed in all cases of breast cancer.
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• No tumour at ink margin on histopathological examination is adequate for BCS in invasive breast carcinoma.
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SYSTEMIC THERAPY

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Risk categories of breast cancer for adjuvant systemic therapy

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
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<tbody>
<tr>
<td>pN0 and all of the following criteria:</td>
<td>pN0 and at least 1 further criterion:</td>
<td>pN+ (N1 - 3) and HER2 overexpression or pN+(N≥4)</td>
</tr>
<tr>
<td>• size of tumour maximum 2 cm</td>
<td>• size of tumour &gt;2 cm</td>
<td></td>
</tr>
<tr>
<td>• Grade 1</td>
<td>• Grade 2/3</td>
<td></td>
</tr>
<tr>
<td>• no vessel invasion</td>
<td>• vessel invasion</td>
<td></td>
</tr>
<tr>
<td>• ER/PR+</td>
<td>• HER2 overexpression</td>
<td></td>
</tr>
<tr>
<td>• HER2-negative</td>
<td>• age &lt;35 years old</td>
<td></td>
</tr>
<tr>
<td>• age ≥35 years old</td>
<td>• pN+ (N1 - 3) and HER2-negative</td>
<td></td>
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</tbody>
</table>
Systemic therapy for metastatic disease

• 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.
• Combination chemotherapy may be considered in fit metastatic breast cancer patients with impending visceral crisis or when rapid resolution of symptoms is required.
• Bisphosphonates may be offered in breast cancer patients with bone metastases to reduce skeletal-related events.

RADIOThERAPY

• Indication for adjuvant radiotherapy:
  i. BCS with clear margin
  ii. Post-mastectomy
    o ≥1 LN positive o positive margin not amenable for surgery o LN negative in T3 or T4

FAMILIAL BREAST CANCER

Comprehensive guidelines for genetic testing are contained in the CPG. However, the simplified Mainstreaming Cancer Genetics Cancer-Based Criteria below may be used as a guide to identify at-risk individuals for evaluation of genetic testing.

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

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

FOLLOW-UP

• Regular follow-up visits are recommended every 3 - 4 months in the first 2 years, every 6 - 8 months from subsequent years 3 - 5 & annually thereafter. The interval of visits should be adapted to the risk of relapse & patients’ needs.

SUPPORTIVE TREATMENT

The following additional management is important & should be considered for breast cancer patients when indicated:

  o psychosocial assessment & intervention  o palliative care
  o breast care nurse  o patient navigation programme
  o lifestyle modifications  o breast cancer patient support groups
ALGORITHM 1. MANAGEMENT OF EARLY BREAST CANCER

Early breast cancer

Surgery

Neoadjuvant systemic therapy

Breast

Mastectomy ± reconstruction

Breast conserving surgery (BCS) + whole breast irradiation

Surveillance (if adjuvant therapy not indicated)

Adjuvant therapy*

Chemotherapy ± anti-HER2 therapy

Radiotherapy

Endocrine therapy

Axilla

Clinical lymph node positive

Axillary clearance

Clinical lymph node negative

Sentinel lymph node biopsy positive

≤2

Axillary clearance

>2

If BCS

No further axillary surgery but axillary radiotherapy may be considered

If mastectomy

Axillary radiotherapy/axillary clearance

*Indication for adjuvant radiotherapy:
  i. BCS with clear margin
  ii. Post-mastectomy
    - ≥1 lymph node positive
    - lymph node negative in T3 or T4
    - positive margin not amenable for surgery

Surveillance (if adjuvant therapy not indicated)

Applications: Breast cancer patients in the management of breast cancer.}

Breast cancer is a systemic disease. Hence, systemic therapy and/or surgery is the mainstay of treatment for early breast cancer, consisting of breast conserving surgery (BCS) + whole breast irradiation or mastectomy ± reconstruction.

Triple assessment which consists of clinical assessment, imaging [ultrasound (US)] and/or mammography & pathology (histology and/or cytology) is required in breast cancer patients when indicated. The cause of the vast majority of breast cancers remains unknown. However, breast cancer is associated with increasing age, family history of breast cancer at a young age, hormonally influenced factors like increased use of hormone replacement therapy, lack of breastfeeding, radiation exposure, physical inactivity, etc. Hormonal factors like oral contraceptive use in hysterectomised women, anti-estrogen use in hysterectomised women have been implicated in the causation of breast cancer. The risk of developing breast cancer increases with age. Hence, early menarche (≤12 years old) or late menopause (>45 years) is a risk factor for breast cancer. For patients with symptoms & signs of breast cancer, mammography may be performed. The breast cancer patient should be referred to breast clinic within 2 weeks. Screening mammography for breast cancer may be performed biennially in women aged 50 - 74 years in the general population. For those with high risk, mammography may be offered in breast cancer patients with bone metastases to reduce skeletal-related events. Therefore, increasing awareness is important for early detection.

Radiation exposure and/or hormone receptor positive, HER2-negative metastatic breast cancer unless there is evidence of visceral crisis or endocrine resistance. Individuals with pathogenic/likely pathogenic variants in BRCA1 & BRCA2 have initial risk evaluation in order to determine if formal risk assessment in a specialist. Breast imaging reporting and data system (BI-RADS®) is the preferred reporting method in the management of breast cancer.

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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
ALGORITHM 2. MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer
- Operable
  - Mastectomy & axillary surgery
  - Neoadjuvant chemotherapy ± anti-HER2 therapy
    - Operable
      - Breast conserving surgery & axillary surgery
      - Mastectomy & axillary surgery
      - Radiotherapy ± hormone therapy ± trastuzumab
    - Inoperable
      - Individualised treatment
- Inoperable
  - Neoadjuvant chemotherapy ± anti-HER2 therapy
    - Operable
      - Chemotherapy ± trastuzumab
      - Surgery
      - Radiotherapy ± hormone therapy ± trastuzumab
    - Inoperable
      - Chemotherapy ± hormone therapy ± trastuzumab

ALGORITHM 3. MANAGEMENT OF METASTATIC BREAST CANCER

Metastatic breast cancer
- No visceral crisis
  - ER/PR+
    - HER2-Negative
      - Pre-menopausal
        - Endocrine therapy ± Anti-HER2
      - Post-menopausal
        - Endocrine therapy
    - HER2-Positive
      - Chemotherapy ± Anti-HER2
- Visceral crisis
  - ER/PR-
    - HER2-Negative
      - Chemotherapy
    - HER2-Positive
      - Adjunct treatment: Bisphosphonates
      - Consider local treatment (radiotherapy/surgery) if indicated