



2018

# SAUDI BREAST CANCER MANAGEMENT GUIDELINES



National Cancer Center  
(NCC)



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## BREAST CANCER MANAGEMENT GUIDELINES

### EVIDENCE LEVELS:

The following evidence levels (EL) were adopted for this guideline:

(EL-1) High Level: well conducted phase III randomized studies or meta-analysis.

(EL-2) Intermediate Level: good phase II data or phase III trials with limitations.

(EL-3) Low Level: observational/ retrospective study/ expert opinions.

### I. ALL BREAST CANCER PATIENTS

#### 1.1 INITIAL PATIENT ASSESSMENT

1.1.1 Obtain detailed clinical assessment including family history; complete physical examination, and document performance status.

1.1.2 Risk assessment (Appendix 1)

1.1.3 Perform the following laboratory tests: Complete blood count (CBC), differential, liver function test (LFT), renal function, hepatitis profile, electrolytes, calcium, alkaline phosphatase, magnesium, phosphorus; vitamin D $\pm$  level.

1.1.4 Bilateral mammogram, + US breast, + MRI breast, if needed (Appendix 2).

1.1.5 Tumor Marker (Clip) to be inserted if tumor size is > 2 cm.

#### 1.2 DIAGNOSIS

1.2.1 Confirm detailed histological and tumor marker diagnosis of breast cancer (Appendix 3) for minimal requirement.

1.2.2 BRCA I/ II/ when indicated and when indicated (Detailed guideline attached).

1.2.3 Genetic counselling if patient is high risk for hereditary breast cancer especially in women younger than age 40.

Consider Fertility counselling if appropriate

1.2.4 Outside pathology to be reviewed if inadequate repeat.

### 1.3 STAGING WORK-UP: (Appendix 4)

#### 1.3.1 Early breast cancer disease (stage I, stage IIA)

- Chest x-ray
- U/S liver

However, every patient will be staged individually based on signs, symptoms, and pathological criteria, for high risk pathology such as TNBC, HER-2 positive BC, then staging will be as in 1.3.2.

#### 1.3.2 Stage IIB/ III

- CT chest, abdomen & pelvis
- Bone scan
- CT/ MRI brain if symptomatic
- (FDG-PET)/CT may be useful when conventional methods are inconclusive

#### 1.3.3 Stage IV disease

- CT chest, abdomen & pelvis
- Bone scan
- CT/ MRI brain if:
  1. Symptomatic patient
  2. Extensive visceral disease, special interest in HER2 + and/or TNBC
- FDG-PET/CT may be useful when conventional methods are inconclusive

#### 1.3.4 Indication for Sentinel lymph node:

- Clinical stage I/ II/ IIIA: Preferable before neoadjuvant chemotherapy
- Sentinel node negative: Consider no further surgery
- Sentinel node positive: Axillary dissection levels I/II
- Sentinel node not identified: Axillary dissection levels I/II.

#### 1.3.5 Clinical node palpable at time of diagnosis:

- FNA or core biopsy if negative, consider no further surgery after discussion on MDTB FNA or core biopsy positive: Axillary dissection levels I/II

### 1.4 PRE-TREATMENT ASSESSMENT

#### 1.4.1 Discuss all new cases in the multidisciplinary conferences.

#### 1.4.2 Echocardiogram or MUGA scan if age >60, or high-risk patients such long standing (diabetics or hypertensive) or HER2 +ve patients

#### 1.4.3 General

- Offer available clinical research studies
- Asses family risk for genetic counselling
- Considers psychosocial assessment
- Consider fertility counselling if indicated
- Psychological and social support

1.4.4 Final TNM staging based on pathology if post-surgery, otherwise clinical staging as per TNM (Appendix 5).

## II. BREAST CANCER

### 2.1 DUCTAL CARCINOMA IN SITU (DCIS): Tis N0M0

2.1.1 Definitive surgery with lumpectomy with 1 cm (10mm) negative margin or mastectomy with or without sentinel node biopsy for patients with high risk features (multiplicity, high grade)

2.1.2 Radiation therapy post breast conservative therapy

2.1.3 For those with ER-positive DCIS, consider Tamoxifen for risk reduction for ipsilateral and contra lateral breast

2.1.4 Post excision mammogram in 6 months then annually

### 2.2 LOBULAR CARCINOMA IN SITU (LCIS): Identified on breast biopsy

2.2.1 If initial biopsy was core needle biopsy: perform surgical excision

2.2.2 If initial biopsy was surgery 4 consider surveillance except for pleomorphic LCIS where complete surgical excision with negative margin should be done (treatment is similar to DCIS)

Counselling for risk reduction

## III. TREATMENT OF EARLY STAGE INVASIVE BREAST CANCER (STAGE I, IIA)

### 3.1 LOCAL THERAPY

#### 3.1.1 Surgery

- Breast conserving surgery with sentinel node biopsy followed by axillary dissection if positive by H&E.

Contraindication for SNB:

- +ve lymph node, FNA/ biopsy
- Inflammatory breast cancer.
- Prior axillary surgery.

Contraindication of BCS:

- A relatively large lesion in a small breast.
- Extensive in situ >25%.
- Multicentric tumor/ multifocal.
- Persistent positive margin after resection.
- Inflammatory BC.

#### 3.1.2 Radiation therapy

- All women who are treated with breast-conserving surgery should have radiation therapy and supraclavicular fossa if node +ve.
- Radiation therapy should follow chemotherapy when chemotherapy is indicated.

Indication for radiation therapy post mastectomy:

- a. Chest wall radiation therapy
  - Node +ve disease.
  - $\geq$  T3 (5 cm).
  - Positive margin or close margin (<1mm).
- b. Supraclavicular radiation therapy
  - Node +ve disease specially if >3 nodes.
- c. Axillary radiotherapy
  - Incomplete axillary dissection.
  - Patient with axillary sampling.
  - Extracapsular invasion.

### 3.2 Systemic Therapy

- Assess patient risk. As per Saint Gallen's risk category (Appendix 6).
- The cut-off point between high and low values for Ki67 varies between laboratories. \*\*Suggested values are 20% for both PgR and Ki67.

(Luminal A), ER-positive, HER2-negative, Ki67 low and PgR high (all should be present)

- Consider ordering Onco-Type DX
- ET alone in the majority of cases
- Consider CT in; high tumour burden (four or more positive LN, T3, higher grade or high Recurrence score (RS) as per Onco-Type DX

#### 1. Pre-menopausal:

- Tamoxifen
- Zoladex (Goserelin) in case of medical contraindication to Tamoxifen

#### 2. Post-menopausal: consider ordering OncoType-DX

- Aromatase inhibitors (AI)
- Tamoxifen

If CT is considered 4 cycles of AC or EC are reasonable options.

### Luminal B Breast cancer:

Luminal B-like (HER2- negative); ER-positive, HER2-negative and either Ki67 high or PgR low

ET + CT are indicated for the majority of cases

**1. Pre-menopausal:**

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane.
2. TC (Taxotere/ Cyclophosphamide) if Anthracycline Contraindicated.
3. Adjuvant hormonal therapy: Tamoxifen for 5 -10 years.
4. In patients < 35 years LHRH agonist + Exemestane is an option.

**2. Post-menopausal:**

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen
2. TC (Taxotere/Cyclophosphamide) if Anthracycline is contraindicated
3. Adjuvant hormonal therapy:
  - a. Tamoxifen for 2-3 years followed by AI.
  - b. Tamoxifen for 5 years followed by AI for 5 years.
  - c. AI for 5 years.

Luminal B-like (HER2- positive); ER-positive, HER2-positive, any Ki67, any PgR

CT + anti-HER2 + ET for all patients

**1. Pre-menopausal**

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen and Trastuzumab for 1 year.
2. TCH (Taxotere/ Carboplatin/ Herceptin) if Anthracycline is Contraindicated.
3. Adjuvant hormonal therapy: Tamoxifen for 5 years + ovarian Ablation.

**2. Post-menopausal**

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen and Trastuzumab for 1 year.

**Notes**

- Trastuzumab should be started in parallel with Taxane and then to continue for adjuvant for 1 year with regular follow-up for cardiac status (Appendix 7)
- For small Her-2 Positive ER positive BC; the following can be adopted o Microinvasive or T1 <.05 cm
  - NO; ET + Herceptine
  - N1mi; ET + Herceptine or TCH X 4 cycles followed by adjuvant ET & Herceptin o T1 .06-1 cm CT + Herceptin as above.

HER2-positive overexpression, HER2-positive, ER and PgR absent

CT + anti-HER2 for all patients

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen and Trastuzumab for 1 year.
2. TCH (Taxotere/ Carboplatin/ Herceptin) if Anthracycline is contraindicated.

Triple-negative; ER negative, PgR negative and HER2-negative

Chemotherapy for all patients except in tumors <.05 cm and NO disease where chemo can be omitted.

1. 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen and Trastuzumab for 1 year.
2. TCH (Taxotere/ Carboplatin/ Herceptin) if Anthracycline is contraindicated.

#### IV. TREATMENT OF LOCALLY ADVANCED INVASIVE BREAST CANCER INFLAMMATORY

Stage IIB, IIIA, IIIB

##### 4.1 Work-up

- As in 1.1, 1.2 and 1.3 (Mammogram + US of affected breast should be available as base line)

##### 4.2 Neoadjuvant Chemotherapy for Her2 amplified tumor.

- 4.2.1 Three-Four cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen and Trastuzumab for 1 year if Her2 positive.
- 4.2.2 A pertuzumab-containing regimen can be considered for Her2 enriched breast cancer
- 4.2.3 TCH (Taxotere/Carboplatin/Herceptin) if Anthracycline is contraindicated.

##### 4.3 Neo-adjuvant therapy for Triple negative breast cancer (TNBC)

- 4.3.1 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen.
- 4.3.2 If BRCA is confirmed triple negative, TC should be used, if BRCA is unknown, TC should be considered.

##### 4.4 Neo-adjuvant therapy for Hormonal +ve (luminal A)

- 4.4.1 AI for post-menopausal women.
- 4.4.2 Chemotherapy is an option.

##### 4.5 Assessment response after neoadjuvant chemotherapy.

- 4.5.1 Clinically every cycle.
- 4.5.2 Ipsilateral U/S mid therapy.
- 4.5.3 Ipsilateral U/S / mammography ± MRI at the end of therapy.

Note:

- Change chemotherapy regimen if progress documented clinically by imaging.
- If continue progress, proceed with surgery if feasible.
- If good response, continue chemotherapy all pre-surgery.

#### 4.6 Surgery:

**4.6.1** BCS if applicable or MRM (Cases to be discussed in multidisciplinary tumor board).

**4.6.2** Inflammatory BC-MRM.

#### 4.7 Adjuvant hormonal therapy with Tamoxifen for pre-menopausal and Aromatase

**4.7.1** Inhibitor (AI) for post-menopausal and to consider extended treatment for total of 10 years in selected cases.

#### Follow up of patients treated for early breast Cancer:

- Interval history and physical exam every 4-6 months for 5 years, then every 12months.
- Annual mammography.
- CT/PET CT and MRI imaging should be considered in symptomatic patients as judged appropriate.
- Women on tamoxifen: annual gynaecological assessment every 12 months if uterus present.
- Women on an aromatase inhibitor who experience ovarian failure should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter.
- Assess and encourage adherence to adjuvant endocrine therapy.
- Evidence suggests that active lifestyle, achieving and maintaining an ideal body weight (20-25 BMI) may lead to optimal breast cancer outcomes.

### V. TREATMENT OF RECURRENT DISEASE:

#### 5.1 Local therapy/Regional

- If initial treatment with lumpectomy + radiation therapy (no axillary dissection).
- Completion of mastectomy or second breast conserving surgery.
- If initial treatment with mastectomy + axillary dissection and radiation therapy.
- Surgical resection if possible.
- If initial treatment with mastectomy no prior radiation therapy.
- Surgical resection if possible + radiation therapy to chest wall and supraclavicular and infraclavicular nodes.

#### 5.2 Regional Recurrence

- Axillary recurrence.

### 5.3 Systemic therapy

- Re-assessment of ER, PR, Her2 status and treat accordingly, not hormonal therapy is preferred in hormone sensitive disease.
- In case of loco regional recurrence, which is completely, with no intense of disease, the re-use of adjuvant chemotherapy does not improve overall survival. Although disease free survival was increased in triple negative or ER-ve disease, this should be discussed with patient.
- If the local treatment is not satisfactory, then systemic treatment should be considered.

## VI. METASTATIC BREAST CANCER:

### General considerations

- Metastatic breast cancer (MBC) is generally incurable a treatable but Still a disease, the goals of care are to optimize both length and quality of life.

6.1 The management of MBC should be done by a comprehensive multidisciplinary team to include a specialized oncology nurses. **EL-3**

- Age alone should not determine the type and intensity of treatment, there is tendency to under treat in elderly and over treat in young patients

6.2 The involvement of supportive palliative team should be encouraged done from the time of diagnosis. **EL-3**

6.3 Treatment choice should take into account at least these factors: **EL-3**

- HR & HER-2 status;
- Previous therapies and their toxicities;
- Disease-free interval;
- Tumor burden (defined as number and site of metastases);
- Physiologic age;
- Performance status;
- Co-morbidities (including organ dysfunctions);
- Menopausal status;
- The need for a rapid disease/symptom control;
- Socio-economic and psychological factors;
- Available therapies in the patient's country;
- Patient reference

- 6.4 Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone. PET—CT, if available, may be used (instead of and not on top of CT scans and bone scan), brain imaging should not be routinely performed in asymptomatic patients. **EL-3.**
- 6.5 The clinical value of routine tumor markers measurement is not well established, their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. But a change in tumor markers alone should not be the only drive to initiate a change in treatment. **EL-3.**
- 6.6 Evaluation of response to therapy should generally occur every 2-4 months for ET or after 2-4 cycles for CT. **EL-3.**
- 6.7 A biopsy (preferably providing histology) of a metastatic lesion is strongly recommended to confirm the diagnosis including the biological markers especially HR and HER-2. The use of targeted therapy (ET and/or anti-HER-2 therapy) should always be considered when receptors are positive in at least one biopsy, regardless of timing. **EL-3.**
- 6.8 The true value of the removal of the primary tumor in patients with stage IV breast cancer is currently unknown but it can be considered in selected patients. **EL-3.**
- 6.9 **ER +/-HER-2 negative MBC:**
- Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of visceral crises or endocrine resistance and there is disease needing a fast response. **EL-1**
  - Visceral crisis is defined as severe organ dysfunction as assessed by signs, symptoms, and laboratory studies, leading to a clinical indication for a more rapidly efficacious therapy.
  - Primary endocrine resistance is defined as: a relapse while on the first 2 years of adjuvant ET, or PD within first 6 month of first-line ET for MBC.
  - Secondary (acquired) endocrine resistances defined as: a relapse while on adjuvant ET but after the first 2 years, or a relapse within 12 months of completing adjuvant ET, or PD≥6 months after initiating ET for MBC.

The definitions of endocrine resistance are proposed by a group of breast cancer researchers and are quoted by ESMO. This is proposed to be applied to clinical trials and not clinical practice.

Here is the quote from ESMO guidelines 2014, “Regarding endocrine resistance, an attempt was made to be consistent with a definition reached by a number of investigators involved in breast cancer clinical trials, at a meeting sponsored by NCI held in May 2012 and later approved by the North American Breast Cancer Groups (NABCGs).

It is also important to note that endocrine resistance is a continuum, and that strict definitions are mainly helpful for the clinical trial setting and not necessarily for routine clinical practice.

- Premenopausal women.
- For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice. EL-1.
- The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proven. AI is also a viable option, but absolutely mandates the use of ovarian Suppression/ablation. EL-1.

A randomized trial has shown survival advantage of TAM+OA strong evidence. The data to support AI+OA in metastatic premenopausal women is very scant and limited to abstract of a phase 2 study not even published. The statement makes both as equal option and the data do not support this.

Second line therapy includes ovarian ablation with or without AI or Faslodex and Palbociclib based on Paloma 3.

Third line include progestins.

- Post-menopausal women.
- The preferred 1st line ET for post-menopausal patients is an aromatase inhibitor; this can be argued in view of results of Falcon study and the Paloma study, however, Fulvestrant HD is also an option, and Tamoxifen remains a viable option in selected patients. **EL-1.**
- The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for Post-menopausal patients (except patients relapsing <12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available OS results are still awaited. Initial survival data negative **LoE: 1A.**
- Optimal post-aromatase inhibitor treatment is uncertain, the decision must take into account the relevant toxicities and should be made on a case-by-case basis.

- The addition of CDK4/6 inhibitor palbociclib to Fulvestrant, beyond 1<sup>st</sup> line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal pts, an LHRH-agonist must also be used. **(LoE:1B)**. At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these types of agents and research efforts must continue.
- The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a nonsteroidal AI, since it significantly prolongs PFS, albeit without OS benefit.
- The decision to treat must take into account the individual relevant toxicities associated with this combination and should be made on a case-by-case basis. **(LoE:1B)**.
- It is currently unknown how the different combinations of endocrine + biological agents compare with each other, and with single agent CT. Several trials are ongoing.
- The available options after the first line include:
  - palbociclib + Fulvestrant, **EL-1**;
  - Everolimus + Exemestain, **EL-1**;
  - Fulvestrant, **EL-1**;
  - Another AI (with a different mechanism of action);
  - Megestrol acetate;
  - Tamoxifen.

#### 6.10 HER-2 positive MBC:

- Anti-HER-2 therapy should be offered early to all patients with HER-2+ MBC unless there is contraindication. **EL-1**.
- The choice of the anti-HER-2 agent will depend on availability, the specific anti-HER-2 therapy previously administered, and the relapse-free interval.
- The optimal sequence of all available anti-HER-152 therapies is currently unknown.
- For patients with ER+/HER-2+ MBC for whom ET was chosen over CT, anti-HER-2 therapy + ET should be considered with the initiation of ET. **EL-1** Confusing statement. It is important to highlight that the survival benefit of HER 2 therapy is when it is combined with chemotherapy. Two small studies showed margin benefit when ET is combined with HER 2 therapy. Therefore, the use of ET with HER2 should not be a choice unless

contraindicated or refused by the patient because the significant survival advantage is lost in this case and absolutely is not a high evidence. **EL-1.**

- For patients with HER-2+ MBC for whom CT was chosen as first-line therapy, the combination of CT + trastuzumab and pertuzumab is the preferred treatment option since it is associated with an OS benefit. **EL-1** (Again this should not be a choice as it is standard of care unless brain mets, poor PS, Pt refusal) and beg to disagree with this statement.
- This three-drug regimen should not be continued at progression on this regimen outside clinical trials, but it is acceptable to use pertuzumab beyond the first line in a HER-2 + MBC patient previously untreated with pertuzumab. The optimal therapy after this combination is not known.
- In the second line setting, T-DM1 provides superior efficacy relative to other HER-2-based therapies, it provides an OS benefit over other choices. **EL-1.**
- If TDM-1 is not available as a second line, other viable option includes;
  - ✓ Continuation of trastuzumab in conjunction with another cytotoxic agent.
  - ✓ Change to lapatinib in combination with capecitabine. **EL-1.**
  - ✓ Combination of trastuzumab & lapatinib. **EL-1.**

#### **Chemotherapy for HER-2 negative MBC:**

For patients with HER-2 negative MBC for whom CT was chosen as first-line therapy;

- Sequential monotherapy is the preferred choice for MBC. **EL-1**
- Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control. **EL-1.**
- In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination chemotherapy, single-agent capecitabine, vinorelbine, or eribulin are the preferred choices. **EL-1.**

- Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines.
- If given in the adjuvant setting, a taxane can be re-used as 1st line therapy, particularly if there has been at least one year of disease-free survival. EL-1.
- Duration of each regimen and number of regimens should be tailored to each individual patient. EL-3.
- Usually each regimen should be given until progression of disease or unacceptable toxicity (unacceptable should be 41) Bevacizumab combined with a taxane as 1st line therapy for MBC provides only a moderate benefit in PFS and no benefit in OS; therefore, Bevacizumab can only be considered as an option in selected cases. EL-1.

#### **Specific sites of metastases:**

##### **6.11. Bone metastases:**

- A bone modifying agent (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with MBC and bone metastases. **EL-1.**

##### **Brain metastases**

- Neurological symptoms and signs, which suggest the possibility of spinal cord compression, must be investigated as a matter of urgency. This requires MRI of the whole spine, is recommended method of choice. An emergency decompression and radiotherapy are the treatment of choice when feasible. **EL-1.**
- Patients with a single or a small number of potentially respectable isolated brain metastasis should be treated with surgery or radio surgery.
- Radio surgery with or without whole brain radiotherapy is also an option for some unrespectable brain metastases. **EL-1.**
- Stereotactic RT should be preferred to whole-brain RT for patients with HER-2-positive MBC with limited number of brain metastases as they live for several years because of leukoencephalopathy.
- Patient with extensive systematic metastasis STS with or without WBRT may be a preferred choice.
- WBRT should be considered for extensive brain metastasis.

##### **Liver metastases**

- There are no randomized data supporting the effect of local therapy on survival.
- This should be considered only be proposed in very selected cases of good performance status, with limited liver involvement, no extra-hepatic lesions, after adequate systemic therapy has demonstrated control of the disease.

- There are no data to select the best technique for the individual patient (surgery, stereotactic RT, intra- hepatic CT, or other).

### **Malignant pleural effusions**

- Drainage is recommended in patients with symptomatic, clinically significant pleural effusion.
- Thoracentesis for diagnosis should be performed only if it is likely that it will change clinical management.
- The use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful.
- Systemic treatment with/ without local management is usually needed.

### **Surgery of the primary tumor in stage IV at diagnosis**

- The true value of the removal of the primary tumor in patients with de novo stage IV breast cancer is currently unknown.
- This can be considered in selected patients.  
Provided that clear margins are expected to be obtained and axilla is being treated. **EL-2**

### **6.12 Supportive care:**

- Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan. **EL-1.**
- Expert palliative care including effective control of pain and other symptoms should be a priority to be initiated at the time of the diagnosis of metastatic disease. **EL-1.**

### **6.13 Principles of monitoring metastatic disease**

- Periodic assessment of varied of symptoms, physical examination, routine laboratory tests, imaging studies, and blood biomarkers were appropriate.
- Results of monitoring are classified as response, stable disease, or progression of disease; this should be based on a balance of multiple information.
- The optimal frequency of repeat testing is uncertain, but is should balance the need to detect progressive disease, avoiding unnecessary toxicity of any ineffective therapy, resource utilization, and cost.
- Patients on Endocrine therapy should be assessed clinically every 2-3 months with repeated CT every 2-6 months and bone scan every 4-6 months.
- Patients on chemotherapy should be assessed clinically prior to each cycle with repeated CT every 2-4 cycle and bone scans every 4 cycles.

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**Appendix 1**

**RISK EVALUATION**

Age: <input type="text"/>	Menarche: <input type="text"/>	Height (m): <input type="text"/>	Weight (kg): <input type="text"/>	Measurements:
			BMI: <input type="text"/>	Metric: <input type="checkbox"/> Imperial: <input type="checkbox"/>
Exercise Level:***				
Light: <input type="checkbox"/>				
Moderate: <input type="checkbox"/>				
High: <input type="checkbox"/>				

Nulliparity: <input type="checkbox"/>
Parity: <input type="text"/>
Unknown: <input type="checkbox"/>
Age at first child: <input type="text"/>

Premenopausal: <input type="checkbox"/>	Age at menopause: <input type="text"/>
Perimenopausal: <input type="checkbox"/>	
Postmenopausal: <input type="checkbox"/>	
No information: <input type="checkbox"/>	

HRT Use:	
Never: <input type="checkbox"/>	Length of use (years): <input type="text"/>
5 or more years ago: <input type="checkbox"/>	
Less than 5 years ago: <input type="checkbox"/>	
Current user: <input type="checkbox"/>	

Age at first baby: <input type="text"/>	Breast Feeding:
Duration bet. pregnancy: <input type="text"/>	>6 mos: <input type="checkbox"/>
	<6 mos: <input type="checkbox"/>
	1 - 2 yrs: <input type="checkbox"/>
OCP:	Long duration >5yrs: <input type="checkbox"/>
Before first baby: <input type="checkbox"/>	

Family History (First Degree):			
Mother: Ovarian: <input type="checkbox"/>	Sister: Ovarian: <input type="checkbox"/>		
Bilateral: <input type="checkbox"/>	Bilateral: <input type="checkbox"/>		
BC: <input type="checkbox"/>	BC: <input type="checkbox"/>		
Age: <input type="text"/>	Age: <input type="text"/>		

Show start up screen

Paternal Gran: Ovarian: <input type="checkbox"/>	Maternal Gran: Ovarian: <input type="checkbox"/>
BC: <input type="checkbox"/>	BC: <input type="checkbox"/>
Age: <input type="text"/>	Age: <input type="text"/>

Affected Nieces

Genetic Testing

Paternal Aunts: Ovarian: <input type="checkbox"/>	Maternal Aunts: Ovarian: <input type="checkbox"/>	Daughters: Ovarian: <input type="checkbox"/>
BC: <input type="checkbox"/>	BC: <input type="checkbox"/>	BC: <input type="checkbox"/>
No. <input type="text"/>	No. <input type="text"/>	No. <input type="text"/>
Age: <input type="text"/>	Age: <input type="text"/>	Age: <input type="text"/>

Previous History of:		
BC: <input type="checkbox"/>	DCIS: <input type="checkbox"/>	
Breast Density:		
Raw image: <input type="checkbox"/>	Digital mammogram: <input type="checkbox"/>	
Previous Breast Biopsy:		
Hyperplasia: <input type="checkbox"/>	Atypical Hyperplasia: <input type="checkbox"/>	Ovarian Cancer: <input type="checkbox"/>
Proliferatal Fibrocyptic: <input type="checkbox"/>	LCIS: <input type="checkbox"/>	
Smoking: <input type="checkbox"/>		

\*\*\*

*Light Does not induce sweating unless it's a hot, humid day. There is no noticeable change in breathing patterns.*  
*Moderate Will break a sweat after performing the activity for about 10 minutes. Breathing becomes deeper and more frequent. You can carry on a conversation but not sing.*  
*High Will break a sweat after 3-5 minutes. Breathing is deep and rapid. You can only talk in short phrases.*



## Appendix 2

### Indications for breast MRI testing

- Should be performed and interpreted by an expert breast imaging team.
- The imaging center should have the ability to perform MRI guided needle sampling.

### Clinical indications

1. May be used to define extent of cancer or presence of multifocal or multicentric center.
2. May be helpful for breast cancer evaluation before and after neoadjuvant therapy.
3. May be useful to detect additional disease in women with mammographically dense breast.
4. May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma or with Paget's disease of the nipple with breast primary not identified on mammography and ultrasound.

### Appendix 3

#### Minimal Reporting Guidelines-Breast Carcinoma (Mastectomy & Lumpectomy Specimen)

The Pathology report with breast carcinoma in mastectomy and lumpectomy specimens should at least include all the following items:

- ✚ Side
  - Right or left (if bilateral please describe each side individually).
- ✚ Procedure/ Specimen Type:
  - Lumpectomy, mastectomy +/- axillary dissection.
- ✚ Invasive carcinoma histologic type and variant if applicable
  - See note
- ✚ Greatest linear invasive tumor dimension
  - Solitary/ multiple
  - Specify if more than one focus and state the greatest diameter of each focus.
- ✚ Histologic grade of invasive carcinoma
  - See note
- ✚ Presence or absence of in situ component (DCIS or LCIS)
  - If DCIS present state:
    - Type, grade, presence or absence of necrosis (comedo type necrosis) and extent of DCIS (% of total tumor volume-see reporting DCIS).
- ✚ Lymph vascular invasion
  - State if there is extensive lymphatic/ vascular invasion (>10 lymphatics involved).
  - Specify if dermal lymphatics are involved.
- ✚ Surgical margins (for invasive and in situ)
  - Positive margin (at the inked or within less than 1 mm), close margin (1-2 mm), free margin (>2 mm)
  - State the distance of the closest in mm, and state which margin if possible.
- ✚ Lymph node status
  - X of Y lymph nodes positive for metastatic carcinoma, size of largest metastasis with or without extra nodal tumor spread.
- ✚ Involvement of skin, nipple, or skeletal muscle by invasive carcinoma

- Skin ulceration, dermal invasion, nipple involvement (Paget's disease, stromal invasion).

+ Index microcalcifications

- Present/ absent

+ Status of background breast tissue

- Atypical hyperplasia, benign mass forming lesions

+ Status of estrogen & progesterone receptors, and Her2-neu expression

- FISH for HER2+ +2 on IHC
- Strength and extent of positivity of hormonal receptor
- Her2 testing should be done in an accredited lab

+ pTNM tumor stage

### Minimal Reporting Guidelines-Ductal Carcinoma in Situ (DCIS)

The Pathology report with DCIS alone should at least include all the following items:

+ Type of DCIS

+ Presence or absence of necrosis

+ Grade

- Nuclear grade (1, 2 and 3)

+ Surgical Margins

- State the distance of the closest margin in mm, and state which margin if possible.

+ Presence or absence of microinvasion/ invasion

- State the distance of invasive component from the in-situ source
- State if multiple sites contain micro invasive/ invasion and the maximum distance.

+ Index microcalcifications

+ ER and PR status

## Appendix 4. Staging

Disease stage should be assessed according to the Tumour Node Metastases (TNM) staging system<sup>1</sup>.

### Primary Tumour (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's 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
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 skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

### Regional lymph nodes (clinical)

NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the <i>absence</i> of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the <i>absence</i> of clinically evident level I, II axillary lymph node metastases

N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident 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
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

### **Regional Lymph nodes (Pathological)**

pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cell clusters (ITC))
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the <i>absence</i> of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the <i>absence</i> of axillary lymph node metastases

pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the <i>presence</i> of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the <i>presence</i> of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

### Distant metastases

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

### Anatomic stage/ Prognostic groups

0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0

	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

## Appendix 5

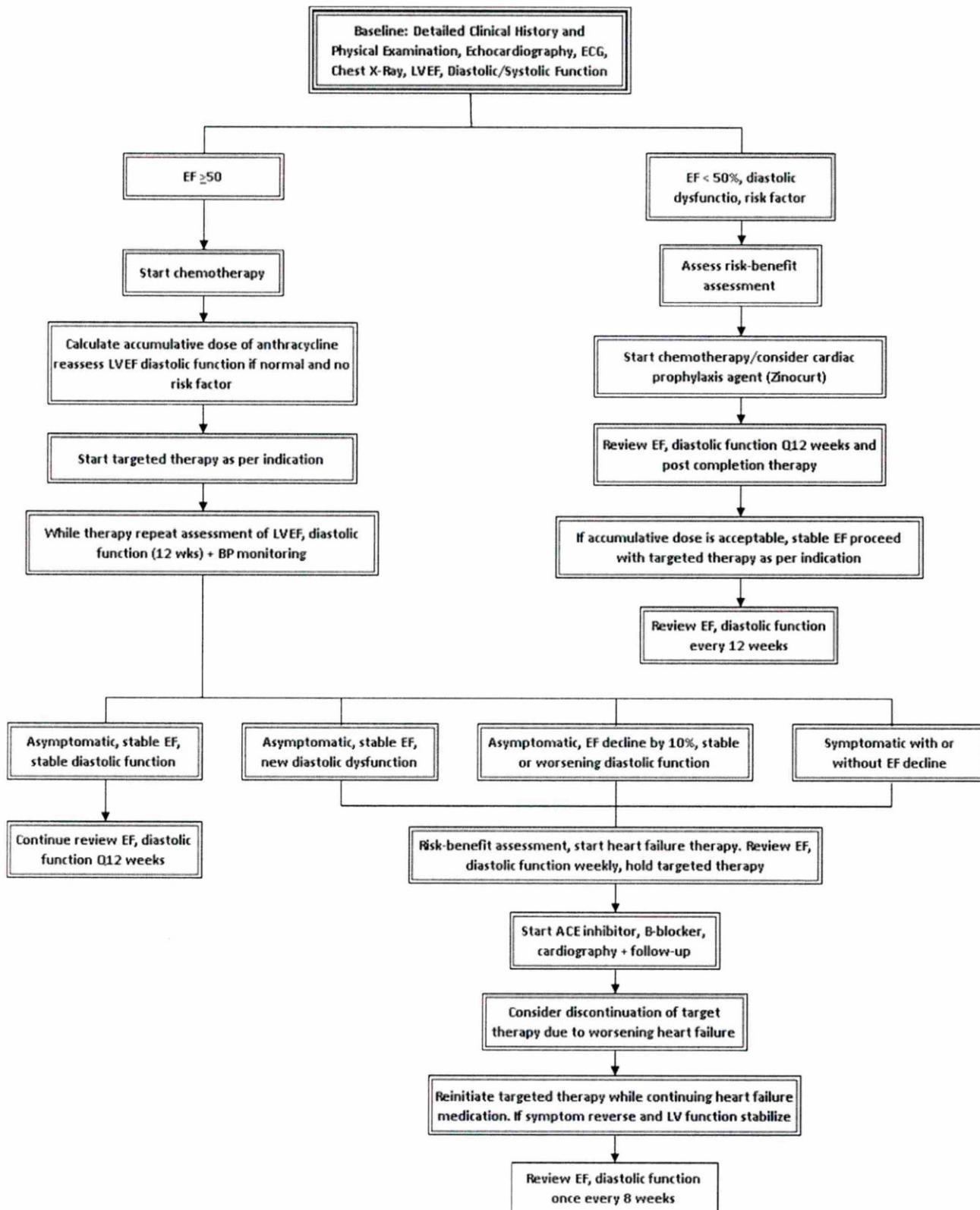
***Risk Categories for Patients with Operated Breast Cancer***

Low Risk	Node-negative and all of the following features	Estimated Risk of recurrence in 10 years (10%)
	<p>pT ≤ 2 cm            Grade 1            Absence of extensive peritumoral vascular invasion            ER and/or PgR expressed            ≥ HER2 gene neither overexpressed nor amplified            Age ≥ 35 years</p>	<10
Intermediate Risk	Node-negative and at least one of the following features	
	<p>pT &gt; 2cm            Grade 2-3            Presence of extensive peritumoral vascular invasion            ER and PgR absent            HER2 gene overexpressed or amplified            Age &lt; 35 years OR            Node-positive (1-3 involved nodes) AND            ER and/pr PgR expressed AND            HER2 gene neither overexpressed nor amplified</p>	10-50
High Risk	Node-positive (1-3 involved nodes) AND	
	<p>ER and PgR absent OR            HER2 gene overexpressed or amplified OR            Node-positive (4 or more involved nodes)</p>	>50



## Appendix 6

### Algorithm for the management of cardiac toxicities



AJCC (American Joint Committee on Cancer). Cancer Staging Manual, 7th edition, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer-Verlag, New York 2010. p.3