SAUDI BREAST CANCER MANAGEMENT GUIDELINES
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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/retrospectives 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, with emphasis on breast size, tumor size, location and lymph nodes status, document performance status (ECOG PS)

1.1.2 Risk assessment for familial breast cancer (optional) (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 level.

1.1.4 Bilateral mammogram, + US breast and Axilla, + MRI breast as indicated (Appendix 2).

1.1.5 Tumor localization (Clip) to be inserted at the time of biopsy.

1.1.6 Consider Fertility counselling if appropriate

1.2 DIAGNOSIS

1.2.1 Confirm histological diagnosis and evaluation of Cell type, grade, hormonal markers (ER, PR), Her2 status, and proliferation index (Ki67). (Appendix 3) for minimal pathological reporting requirement.

1.2.2 Outside pathology to be reviewed and if inadequate to be repeated.

1.2.3 Core biopsy / FNA of Axillary nodes should be considered as per radiological evaluation.
(Appendix 4)

1.3 STAGING WORK-UP:

1.3.1 Early breast cancer
- 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.

Consensus 80% 

1.3.2 locally advanced/ metastatic breast cancer
- CT chest, abdomen & pelvis
- Bone scan
- Additional studies as clinically indicated

1.3.4 Indication for Sentinel lymph node:

Sentinel lymph node is indicated in the setting of clinically/ radiological negative Axilla.

1.4 PRE-TREATMENT ASSESSMENT

1.4.1 Discuss all new cases in the multidisciplinary tumor board meeting.

1.4.2 Echocardiogram or MUGA scan for all HER2 +ve patients planned for HER2 targeted therapy

Age > or equal 55, or high-risk patients such as long standing chronic disease (diabetics or hypertensive).

1.4.3 General
- Offer available clinical research studies
- Consider family risk for genetic counselling
- 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 4)

II. BREAST CANCER

2.1 DUCTAL CARCINOMA IN SITU (DCIS): Tis N0M0) (refer to surgical guidelines for more details)

2.1.1 Definitive surgery with lumpectomy aiming for 1 cm (10mm) negative surgical margins or mastectomy.

Sentinel lymph node biopsy should be considered for patients who will have mastectomy.

2.1.2 Adjuvant Radio therapy post breast conservative surgery as indicated.

Radio therapy can be omitted in low risk patient: DCIS size less than 15 mm, margins more than 10 mm, age more than 60 and low grade DCIS. (see principle of adjuvant radiation therapy)

2.1.3 For those with ER-positive DCIS, Tamoxifen / AI for risk reduction for ipsilateral and contra lateral breast is not optional, preferred.

2.1.4 Post excision mammogram annually

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

2.2.1 in Pleomorphic LCIS, surgical excision is indicated.

2.2.2 for other types of LCIS, follow up is sufficient.
III. TREATMENT OF EARLY STAGE INVASIVE BREAST CANCER

(Upfront surgery planned)

3.1 LOCAL THERAPY

3.1.1 Surgery

- Breast conserving surgery with sentinel lymph node biopsy

Contraindication for SNB:

- Clinically positive biopsy proven lymph node
- Inflammatory breast cancer.

Contraindication of BCS:

- If radiotherapy is contraindicated for any reason
- A relatively large lesion in a small breast.
- Extensive DCIS by imaging.
- Multicentric tumor/ multifocal.
- Inflammatory BC.
- Retro areolar lesion.

3.1.2 Radiation therapy (See Principle of Radiation Therapy)

- All women who are treated with breast-conserving surgery should have radiation therapy.
- Radiation therapy should follow chemotherapy when chemotherapy is indicated.

3.1.2 Radiation therapy

- All women who are treated with breast-conserving surgery should have radiation therapy.
  - Radiotherapy can be omitted in patients age more than 70 years with very low risk of local recurrence AND are willing to take endocrine therapy
  - Tumor bed boost is indicated in patients < 50 years old, or with poor pathological features.
- Patients need to be informed about the side effects, including cosmesis, particularly in women with larger breasts size

- Radiotherapy should be started after wound healing or 3-4 weeks following adjuvant chemotherapy

**Indication for radiation therapy post mastectomy:**

a. Chest wall radiation therapy
   - Node +ve disease.
   - ≥ T3 / T4 disease.
   - Positive margin or close margin (<1mm).

b. supraclavicular nodal radiation therapy
   - >3 positive lymph nodes.
     - 1-3 metastatic axillary LN with other poor prognostic factors.

c. Axillary nodal radiotherapy
   - Incomplete axillary dissection.
   - Patient with axillary sampling.
   - Extracapsular invasion.

**D. Internal Mammary nodal radiation therapy**

- T4 disease
- Medial located tumor with axillary lymph nodes metastasis

**E. Dosing schedule**

- 40-42.5 Gy in 15-16 fractions over 3 weeks
- 45-50.4 Gy in 25-28 Fractions over 5-6 weeks
- Boost dose is 10Gy in 4-5 fractions over one week
- Use bolus as indicated by dosimetric plan where the skin is part of your target volume.
- Treatment breaks should be avoided wherever possible

**3.2 Systemic Therapy**

(Luminal A), ER-positive, HER2-negative, Ki67 low (less than or equal to 20%) (all should be present)

- Consider ordering Onco-Type DX
- Endocrine therapy alone if oncotype DX recurrence score (RS) is less than 25.
- Chemotherapy may be an option for those younger than 50 years old with RS more than or equal 20.
- Consider short course of chemotherapy in; high tumour burden (four or more positive LN, T3, or high Recurrence score (RS) as per Onco-Type DX
1. **Pre-menopausal:**
   - Tamoxifen
   - LHRH - Agonist + Tamoxifen
   - LHRH – Agonist + Al (Examastane) especially in women younger than 35 years old, who received chemotherapy.

2. **Post-menopausal:**
   - Aromatase inhibitors (Al)
   - Tamoxifen

**Luminal B Breast cancer:**

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

ET + CT are indicated for the majority of cases with HER 2 – Luminal B with high recurrence score

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

   CT + anti-HER2 + ET for majority of patients

**Notes**

- Trastuzumab should be started in parallel with Taxane and then to continue for for 1 year with regular follow-up for cardiac status (Appendix 7)
- The standard duration of Trastuzumab is 12 months. However, 6 months may be an alternative option in selected cases.
- For small Her-2 Positive ER positive BC; the following can be adopted Microinvasive or T1 <0.5 cm consider short course of CT and Trastuzmab or neither.
- Endocrine therapy for all

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

Chemotherapy for the majority of patients:

3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen.
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.
   4.1.1 Three-Four cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane + dual anti Her2 then anti Her2 for 1 year.
   4.1.2 TCH (Taxotere/Carboplatin/Herceptin) if Anthracycline is contraindicated.

4.3 Neo-adjuvant therapy for Triple negative breast cancer (TNBC)
   4.2.1 3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen.
   4.2.2 If BRCA is confirmed triple negative, Taxane/platinum based regimen should be used , if BRCA is unknown, TC should be considered.

4.4 Neo-adjuvant therapy for Hormonal +ve (luminal A)
   4.3.1 AI for post-menopausal women.
   4.3.2 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 Radiotherapy (Dr. Yasir new)

Radiotherapy is indicated post neoadjuvant chemotherapy or hormone therapy then mastectomy in
- T3 / T4 disease
- the presence of pathologically positive axillary nodes after neoadjuvant treatment (ypN+)
- positive axillary nodes at presentation even if they become pathologically negative after chemotherapy

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 12 months.
- 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.
5.2 Regional Recurrence

- Axillary recurrence.

5.3 Systemic therapy

- Re-assessment of ER, PR, Her2 status and treat accordingly.
- Hormonal therapy is preferred in hormone sensitive disease.
- In case of loco regional recurrence, which is completely excised, with no systemic disease, there is no evidence that chemotherapy improve overall survival although one study have shown PFS improvement.

- If the local treatment is not satisfactory, then systemic treatment should be considered.

6.1 Workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone scan). Brain imaging should be considered only in symptomatic patients.
6.2 The clinical value of routine tumor markers measurement is not well established, their use (if elevated) as an aid to evaluate response to treatment but changing of management should not be based on tumor marker only.

6.3 Evaluation of response to therapy should generally occur every 3-4 months for ET or after 3-4 cycles for CT.

6.4 A biopsy of a metastatic lesion is strongly recommended especially for long disease free interval.

6.5 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.

6.6 ER +/-HER-2 negative MBC:

- Endocrine based 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.
- 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.
- For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine based therapy is the first choice.

- For Post-menopausal women the preferred 1st line ET is an aromatase inhibitor; the available options include:
  - CDK 4/6 inhibitors + AI
  - Fulvestrant
  - AI
  - Fulvestrant + AI
  - Tamoxifen

- The choice of treatment after the failure of first-line therapy depends on prior therapy; options include:
  - CDK 4/6 inhibitors + Fulvestrant
  - Everolimus + Exemestane
  - Fulvestrant
  - Another AI (with a different mechanism of action)
  - Tamoxifen
  - Megestrol acetate

6.7 HER-2 positive MBC:

6.8 For patients with ER-/HER-2+ MBC, the preferred first-line treatment option is Pertuzumab + Trastuzumab + Taxane. Other options include:
- Trastuzumab Emtansine
- Trastuzumab + chemotherapy
- Trastuzumab + other Anti-HER2 therapy

6.9 For patients with ER+/HER-2+ MBC, the preferred first-line therapy is the combination of CT + trastuzumab and pertuzumab is the preferred treatment option. Following completion of chemotherapy, ET is recommended in addition to anti-HER-2 therapy as maintenance.

6.9.1 For patients with ER+/HER-2+ MBC not considered for chemotherapy, the combination of ET + Anti-HER2 therapy is the preferred option.

6.10 In the second line setting, Trastuzumab Emtansine is the preferred option.

Other options include:
- Trastuzumab + another chemotherapy
- Lapatinib + Capecitabine
- Trastuzumab + Lapatinib
- Anti-HER2 + ET

6.11 Chemotherapy for HER-2 negative MBC:

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

- Sequential single-agent chemotherapy is the preferred option.

- Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

- Immunune therapy can be considered for BRCA negative triple negative breast cancer.

- PARP inhabotir for PRCA mutant

Chemotherapy options include:
- Taxanes
- Anthracyclines
- Capecitabine
- Gemcitabine
- Platinum
- Eribulin
- Ixabepilone
References


## Appendix 1

### RISK EVALUATION

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<tr>
<th>Age:</th>
<th>Menarche</th>
<th>Height (in):</th>
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<td>LCIS:</td>
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<tr>
<td>Ovarian Cancer:</td>
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### Smoking:

***

- **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

Main Clinical indications for Breast MRI

1. To define extent of cancer or presence of multifocal or multicentric.
2. For evaluation before and after neoadjuvant therapy.
3. To detect additional disease in women with mammographically dense breast.
4. 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.

**Primary Tumour (T)**

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<th>Description</th>
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<td>Primary tumor cannot be assessed</td>
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<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
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<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
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<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
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<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
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<tr>
<td>Tis (Paget's)</td>
<td>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.</td>
</tr>
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</table>

**T1**

- **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)**

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

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
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<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>T0</td>
<td>N1mi</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1mi</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
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</tr>
<tr>
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<td>M0</td>
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</tr>
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<td>N1</td>
<td>M0</td>
<td></td>
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<tr>
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</tr>
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<td>N2</td>
<td>M0</td>
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<tr>
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<td>N2</td>
<td>M0</td>
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<tr>
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<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
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</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
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<tr>
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<td>N0</td>
<td>M0</td>
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</tr>
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<tr>
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### Distant metastases

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No clinical or radiographic evidence of distant metastases</td>
</tr>
<tr>
<td>cM0(i+)</td>
<td>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</td>
</tr>
<tr>
<td>M1</td>
<td>Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm</td>
</tr>
<tr>
<td>Stage</td>
<td>T Status</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>
Appendix 5

Algorithm for the management of cardiac toxicities

Baseline: Detailed Clinical History and Physical Examination, Echocardiography, ECG, Chest X-Ray, LVEF, Diastolic/Systolic Function

EF ≥ 50

Start chemotherapy

Calculate accumulative dose of anthracycline, reassess LVEF, diastolic function if normal and no risk factor

Start targeted therapy as per indication

While therapy repeat assessment of LVEF, diastolic function (12 wks) + BP monitoring

Asymptomatic, stable EF, stable diastolic function

Continue review EF, diastolic function Q12 weeks

EF < 50%, diastolic dysfunction, risk factor

Assess risk-benefit assessment

Start chemotherapy/consider cardiac prophylaxis agent (Sinucort)

Review EF, diastolic function Q12 weeks and post completion therapy

If accumulative dose is acceptable, stable EF proceed with targeted therapy as per indication

Review EF, diastolic function every 12 weeks

Asymptomatic, stable EF, new diastolic dysfunction

Risk-benefit assessment, start heart failure therapy. Review EF, diastolic function weekly, hold targeted therapy

Start ACE inhibitor, β-blocker, cardiography + follow-up

Consider discontinuation of target therapy due to worsening heart failure

Reinitiate targeted therapy while continuing heart failure medication. If symptom reverse and LV function stabilize

Review EF, diastolic function once every 8 weeks

Asymptomatic, EF decline by 10%, stable or worsening diastolic function

Symptomatic with or without EF decline