DISCLAIMER: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

NOTE: Consider clinical trials as treatment options for eligible patients.

INITIAL MULTIDISCIPLINARY EVALUATION

- Pathology review
- Bilateral diagnostic mammography
- History and physical
- CBC, platelets, liver function tests (total bilirubin, alkaline phosphatase, transaminases), creatinine
- Diagnostic imaging of breast and regional nodal basins with FNA or core biopsy of suspicious nodes
- Clip placed in nodes with biopsy confirmed metastasis
- In patients with clinical suspicion of distant metastasis body imaging recommended, consider for clinical stage IIIb and III
- Consider need for genetic counseling, fertility preservation, and pregnancy testing
- Pre-operative lymphedema education and screening
- Lifestyle risk assessment

CLINICAL STAGING

- Candidate for breast conservation at presentation?
- Size of nodal metastasis
- Lymphatic/vascular invasion
- ER, PR status
- Margin status
- HER2 status
- Special histologies (i.e., tubular, medullary, pure papillary, or colloid)
- Negative margins
- Resolution of any skin edema after systemic therapy
- No evidence of diffuse calcifications on mammogram
- No contraindication to radiation therapy
- Tumor size
- Lymph node status
- Composite histologic grade
- Pathology review to include:
- Patients with lupus and scleroderma
- Patients with limited life expectancy
- Sarcoma of the breast
- Patients with sarcoma of the breast

TREATMENT

- Breast conservation therapy with sentinel lymph node (SLN) surgery or
- Total mastectomy with SLN surgery with or without reconstruction
- Consider neoadjuvant chemotherapy for biologically aggressive tumors when appropriate, place radio-opaque markers in primary tumor
- Breast conservation therapy with axillary surgery or
- Total mastectomy with axillary lymph node surgery with or without reconstruction
- Consider neoadjuvant chemotherapy or neoadjuvant endocrine therapy
- Confirm placement radio-opaque markers
- Total mastectomy with SLN surgery with or without reconstruction

1 There are special circumstances in which these guidelines do not apply. These include, but are not limited to:
- Patients with lupus and scleroderma
- Patients with sarcoma of the breast

2 Pathology review to include:
- Tumor size
- Lymph node status
- Composite histologic grade
- Pathologic type
- Cancer during pregnancy
- Special histologies (i.e., tubular, medullary, pure papillary, or colloid)
- Negative margins
- Resolution of any skin edema after systemic therapy
- No evidence of diffuse calcifications on mammogram

3 Consider MD Anderson approved breast biomarkers

6 Candidates for breast conservation therapy: Tumor to breast size ratio allows for acceptable cosmetic result No evidence of diffuse calcifications on mammogram

7 Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of greater than 85% and a false negative rate of less than 5%) may consider sentinel lymph node surgery as the initial and primary means of evaluating nodal status for selected patients who are clinically node negative.

8 For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is preferred. Preoperative consultation with Plastic Surgery and Radiation Oncology recommended.

9 See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options

10 Radio-opaque markers should be placed as close to initiation of therapy as possible if not done at time of diagnosis

11 See Appendix D - Endocrine Systemic Adjuvant Therapy Options

12 Candidates for limited axillary surgery with a prior biopsy proven axillary lymph node metastasis must have documented removal of the prior biopsied and clipped lymph node. Preferred approach is targeted axillary dissection which includes SLN with selective localization and removal of clipped node.

Approved by Executive Committee of the Medical Staff on 02/27/2018
NOTE: Consider clinical trials as treatment options for eligible patients.

**POST-SURGERY**

**PATHOLOGIC STAGING**

- **Meets Z0011 criteria?**
  - Yes → **No further axillary surgery**
  - No → **Completion axillary lymph node dissection (ALND)**

- **Positive nodes?**
  - Yes → **Tumor less than or equal to 0.5 cm**
    - **Consider endocrine therapy** if tumor is hormone receptor positive
    - **Consider anti-HER2 based therapy** if HER2-positive
  - No → **Tumor greater than 0.5 to 1 cm**
    - **Consider multi-gene prognostic assays**
    - **Consider adjuvant chemotherapy** for adverse prognostic features
    - **Use anti-HER2 based therapy** for HER2-positive disease
    - **Adjuvant endocrine therapy** if tumor is hormone receptor positive
  - **Tumor greater than 1 cm**
    - **Consider multi-gene prognostic assays**
    - **Consider adjuvant chemotherapy** when appropriate
    - **Anti-HER2 based therapy** for HER2-positive disease
    - **Adjuvant endocrine therapy** if tumor is hormone receptor positive

**ADJUVANT THERAPY FOLLOWING SURGERY AS LOCAL TREATMENT**

- **Adjuvant chemotherapy** with anthracycline/taxane-based regimen
- **Anti-HER2 based therapy** regimen if HER2-positive
- **Adjuvant endocrine therapy** if tumor is hormone receptor positive

See Page 4 for Radiation Therapy Options

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1. **Z0011 criteria**: Clinical T1 or T2, N0, M0, lumpectomy and sentinel lymph node surgery, and tumor positive sentinel node (up to two nodes positive on sentinel node surgery) planned for whole breast irradiation and systemic therapy
2. See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options
3. Cardiac evaluation at baseline and as clinically indicated
4. See Appendix D - Endocrine Systemic Adjuvant Therapy Options
5. Lymphovascular invasion (LVI), triple receptor negative, high grade
6. Tumors of favorable histology less than 3.0 cm (tubular, mucinous) can be considered lower risk and treated appropriately
Breast Cancer – Invasive

Clinical Stage/ Presentation

- Assess tumor size at least every 6 weeks and at completion of systemic treatment with physical exam
- Imaging (mammogram, ultrasound, and MRI if indicated) at completion of systemic treatment, if undergoing breast conserving surgery
- Consider mid-treatment ultrasound or other imaging at any point for clinical suspicion of disease progression
- If clinical progression, proceed with surgery, or change to alternate salvage therapy if unresectable, and then follow local treatment guidelines and systemic adjuvant therapy guidelines

Local Treatment

Breast Conserving Surgery

- If clinically node negative at diagnosis, proceed with sentinel node surgery followed by axillary node surgery if sentinel node is positive
- If clinically node positive, confirmed by needle biopsy proceed with axillary node dissection or if axillary nodal disease limited at presentation and is no longer evident, consider SLN biopsy with documented removal of clipped node and if no metastases proceed to radiation therapy without axillary lymph node dissection

Total mastectomy with nodal treatment as determined by initial nodal status:

- If clinically node negative at diagnosis, proceed with sentinel node biopsy followed by axillary node surgery if sentinel node positive
- If clinically node positive, confirmed by needle biopsy proceed with axillary node dissection or if limited axillary nodal disease at presentation and no longer evident on imaging consider SLN biopsy with documented removal of clipped node and if no metastases proceed to radiation therapy without axillary lymph node dissection
- Consider reconstruction and plastic surgery consult

1 See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options
2 See Appendix D - Endocrine Systemic Adjuvant Therapy Options. Higher risk patients could be considered for post-operative chemotherapy.
3 Candidates for breast conservation therapy:
- Tumor to breast size ratio allows for acceptable cosmetic result
- Negative margins
- Resolution of any skin edema after systemic therapy
- No evidence of diffuse calcification on mammogram
- No contraindication to radiation therapy
4 Cardiac evaluation at baseline and as clinically indicated
5 Neoadjuvant response assessment with MRI in cases where mammogram and/or ultrasound are insufficient
6 Limited nodal involvement at presentation is defined as 3 or fewer abnormal nodes on axillary ultrasound. Any biopsy proven positive node should be clipped at presentation and documentation of clipped nodes is required at surgery.
7 Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of greater than 85% and a false negative rate of less than 5%) may consider sentinel lymph node dissection as the initial and primary means of evaluating nodal status for selected patients who are clinically node negative
8 For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is preferred.

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NOTE: Consider clinical trials as treatment options for eligible patients.
NOTE: Consider clinical trials as treatment options for eligible patients.

**PATHOLOGIC FINDINGS**

- Stage I - II disease, with 0-3 involved lymph node(s)
  - Whole breast radiation therapy for breast conservation therapy with or without regional lymphatics
- Consider partial breast radiation therapy for tumors less than or equal to 3 cm and negative lymph nodes
- Radiation consult for consideration of chest wall radiation therapy with or without regional lymphatics for patients with total mastectomy and tumor greater than 5 cm or any positive lymph nodes

- Stage III disease or 4 or more involved lymph nodes
  - Post mastectomy radiation therapy to chest wall and regional lymphatics
  - Whole breast radiation therapy with regional lymphatics for breast conservation therapy

**TREATMENT**

- Whole breast radiation therapy for breast conservation therapy with or without regional lymphatics
- Consider partial breast radiation therapy for tumors less than or equal to 3 cm and negative lymph nodes
- Radiation consult for consideration of chest wall radiation therapy with or without regional lymphatics for patients with total mastectomy and tumor greater than 5 cm or any positive lymph nodes

- Endocrine therapy for hormone receptor positive tumors sequential after chemotherapy
- Trastuzumab plus or minus pertuzumab to complete one year if HER2-positive tumor
- Consider neratinib for one year as extended adjuvant therapy for Stage II or higher HER2-positive disease within 1-2 years (preferably 1) after completion of maintenance trastuzumab plus or minus pertuzumab maintenance
- For residual invasive disease after neoadjuvant therapy, can consider additional systemic therapy: current evidence exists for the addition of capecitabine for six to eight cycles

**SURVEILLANCE**

- Physical exam at least every 3-6 months for 5 years, then annually after year 5
- If breast conservation therapy, mammogram of treated breast at 6-12 months, then annually
- Annual gynecologic exam, if receiving tamoxifen
- Assess bone health (see Breast Cancer Survivorship: Bone Health Algorithm)
- Encourage age appropriate cancer and general health guidelines
- Educate, screen and refer for lymphedema management as needed

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1. Radiation therapy for BCT and post-mastectomy radiation, are generally delivered at completion of chemotherapy. For early stage node negative patients, radiation therapy may be delivered before or after chemotherapy.
2. See Appendix D - Endocrine Systemic Adjuvant Therapy Options
3. See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options
4. Trastuzumab plus or minus pertuzumab can be administered concurrently with endocrine therapy.
Biopsy to confirm metastatic disease, histology, ER/PR and HER2 status

Bone scan

CT, PET/CT or MRI to encompass chest, abdomen and pelvis

Consider chest x-ray if no CT is performed

Complete blood count and chemistries including renal and liver function

Consider tumor markers as an adjunctive test for monitoring response to therapy

Distant metastasis

- Biopsy to confirm metastatic disease, histology, ER/PR and HER2 status
- Bone scan
- CT, PET/CT or MRI to encompass chest, abdomen and pelvis
- Consider chest x-ray if no CT is performed
- Complete blood count and chemistries including renal and liver function
- Consider tumor markers as an adjunctive test for monitoring response to therapy

EVALUATION FOR METASTASIS

Pre-menopausal endocrine options

- Tamoxifen with or without ovarian ablation
- In premenopausal patient following ovarian ablation use post-menopausal endocrine options

Aromatase inhibitor (AI) with or without palbociclib, ribociclib or abemaciclib
- If no prior endocrine therapy (including adjuvant), can consider fulvestrant or AI with fulvestrant
- Tamoxifen (if no prior tamoxifen)

TREATMENT FOR METASTASIS

Second line therapy (or within one year of completing adjuvant endocrine therapy with aromatase inhibitor)

- Exemestane with or without everolimus
- Fulvestrant with or without palbociclib or abemaciclib (if fulvestrant not given previously)
- Consider olaparib for patients with germ line BRCA mutation

Third or Later Line of Therapy

Other endocrine or biological treatments:

- Estrogens
- Progestins
- Androgens
- Abemaciclib
- Consider olaparib for patients with germ line BRCA mutation

Chemotherapy until progressive disease or maximum benefit can include:

- Anthracyclines based upon lifetime exposure to anthracyclines
- Capecitabine
- Carboplatin
- Cisplatin
- Eribulin
- Taxanes
- Gemcitabine
- Vinorelbine
- Ixabepilone

Targeted therapy: Consider olaparib for patients with germ line BRCA mutation

NOTE: All patients with bone metastases and life expectancy greater than 12 weeks should consider after dental evaluation: a bisphosphonate (creatinine clearance is 30 or greater) or denosumab.

Continue current treatment until progressive disease or unacceptable toxicity then consider alternate endocrine therapy

Disease response or clinical benefit?

Yes

No

Failure to respond to multiple sequential regimen or Zubrod status greater than or equal to 3, discontinue chemotherapy

Palliative care

HER2-negative

ER positive and bone or soft tissue metastasis only or limited visceral disease

Post-menopausal endocrine options

HER2-positive by either immunohistochemistry 3+ or FISH

See Page 6

1 See Appendix B - Scenarios requiring individualized therapy

2 See Appendix D - Endocrine Systemic Adjuvant Therapy Options. Male patients should be treated similarly to premenopausal patients.

3 Consider breast surgery for patients with limited responding metastatic disease who have an intact primary

4 See Appendix C - Recurrent or Metastatic Breast Cancer Treatment Options

Use of aromatase inhibitors or fulvestrant should be accompanied by androgen deprivation therapy (medical/surgical).

NOTE: Consider clinical trials as treatment options for eligible patients.
**Breast Cancer – Invasive**

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**NOTE:** Consider clinical trials as treatment options for eligible patients.

**TREATMENT FOR METASTASIS**

If no prior trastuzumab or greater than 1 year since adjuvant trastuzumab:
- Taxane chemotherapy plus trastuzumab plus pertuzumab
- Alternate therapy based on hormone receptor status if not candidate for anti-HER2 or cytotoxic therapy

If less than 6 to 12 months from adjuvant trastuzumab or if prior (neo)adjuvant pertuzumab:
- T-DM1 (Ado-trastuzumab emtansine)
- Consider alternate HER2 directed therapies

**Progressive disease**

Proceed to one of the following regimens, and can follow by another regimen below if the patient continues to be a candidate for antineoplastic therapy:
- T-DM1 if not previously given
- Capecitabine plus lapatinib
- Trastuzumab plus lapatanib
- Trastuzumab plus other chemotherapy (preferred options - vinorelbine, gemcitabine, capecitabine, eribulin)
- Chemotherapy or hormonal therapy (if ER or PR positive)
- Trastuzumab plus pertuzumab (if pertuzumab not previously given)
- Other HER2 directed therapies

**Failure to respond to multiple sequential regimens or Zubrod status greater than or equal to 3, discontinue chemotherapy**

**Palliative care**

**NOTE:** All patients with bone metastases and life expectancy greater than 12 weeks should consider after dental evaluation: a bisphosphonate (creatinine clearance is 30 or greater) or denosumab.

HER2-positive by either immunohistochemistry 3+ or FISH, (HER2/CEP17 ratio greater than or equal to 2 or HER2 copy number greater than or equal to 6)

**ER = Estrogen Receptor  FISH = Fluorescence In Situ Hybridization  HER2 = Human Epidermal Growth Factor Receptor 2  PR = Progesterone Receptor**

1 See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options

2 See Appendix C - Recurrent or Metastatic Breast Cancer Chemotherapy/Biotherapy Treatment Options

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Breast Cancer – Invasive

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NOTE: Consider clinical trials as treatment options for eligible patients.

EVALUATION FOR LOCAL RECURRENCE

TREATMENT FOR RECURRENCE

Ipsilateral breast/chest wall recurrence or ipsilateral regional nodal recurrence without distant metastasis

Previous breast radiation therapy?

Yes →

Biopsy to confirm recurrence with:

- If intact breast, bilateral diagnostic mammogram
- Ultrasound of affected breast including regional nodal basins
- Consider body imaging for invasive recurrence
- Consider preoperative systemic therapy
- Consider biomarkers1 of breast/chest wall recurrence or nodal recurrence (if no breast/chest wall recurrence)

Breast intact?

Yes →

Endocrine therapy or HER2-directed therapy with or without chemotherapy2

No →

Resectable?

Yes →

Surgical resection with margin assessment

No →

Endocrine therapy1 or HER2-directed therapy with or without chemotherapy2

Resectable?

Yes →

Radiation therapy to chest wall and regional lymphatics, if no previous radiation

No →

Persistent disease?

Yes →

Consider systemic therapy2,3,4

No →

Consider additional systemic therapy2,3,4

Resectable?

Yes →

Previous chest wall radiation therapy?

Yes →

Consider systemic therapy2,3,4

No →

Surveillance and endocrine therapy if estrogen receptor positive3,4

Consider radiation therapy

No (e.g., DCIS)

Invasive histology?

Yes →

Consider systemic therapy2,3,4

No →

Surveillance and endocrine therapy if estrogen receptor positive3,4

Consider radiation therapy

Consider pre-operative chemotherapy2

Total mastectomy with lymph node surgery consider sentinel lymph node surgery if clinically node negative

Total mastectomy; lymph node surgery; radiation therapy consult

Breast conservation therapy with margin assessment, or

Wide local excision (WLE) with margin assessment

Consider neoadjuvant systemic therapy prior to WLE

Consider systemic therapy2,3,4

Radiation therapy to chest wall, and regional lymphatics (if not DCIS alone)

Consider systemic therapy2,3,4

Endocrine therapy1

Yes

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1 Consider MD Anderson approved Breast biomarkers
2 See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options
3 See Appendix D - Endocrine Systemic Adjuvant Therapy Options
4 Surveillance upon completion of all therapy

NOTE 1:

EVALUATION FOR LOCAL RECURRENCE

Ipsilateral breast/chest wall recurrence or ipsilateral regional nodal recurrence without distant metastasis

Previous breast radiation therapy?

Yes →

Biopsy to confirm recurrence with:

- If intact breast, bilateral diagnostic mammogram
- Ultrasound of affected breast including regional nodal basins
- Consider body imaging for invasive recurrence
- Consider preoperative systemic therapy
- Consider biomarkers1 of breast/chest wall recurrence or nodal recurrence (if no breast/chest wall recurrence)

Breast intact?

Yes →

Endocrine therapy or HER2-directed therapy with or without chemotherapy2

No →

Resectable?

Yes →

Surgical resection with margin assessment

No →

Endocrine therapy1 or HER2-directed therapy with or without chemotherapy2

Resectable?

Yes →

Radiation therapy to chest wall and regional lymphatics, if no previous radiation

No →

Persistent disease?

Yes →

Consider systemic therapy2,3,4

No →

Consider additional systemic therapy2,3,4

Resectable?

Yes →

Previous chest wall radiation therapy?

Yes →

Consider systemic therapy2,3,4

No →

Surveillance and endocrine therapy if estrogen receptor positive3,4

Consider radiation therapy

No (e.g., DCIS)

Invasive histology?

Yes →

Consider systemic therapy2,3,4

No →

Surveillance and endocrine therapy if estrogen receptor positive3,4

Consider radiation therapy

Consider pre-operative chemotherapy2

Total mastectomy with lymph node surgery consider sentinel lymph node surgery if clinically node negative

Total mastectomy; lymph node surgery; radiation therapy consult

Breast conservation therapy with margin assessment, or

Wide local excision (WLE) with margin assessment

Consider neoadjuvant systemic therapy prior to WLE

Consider systemic therapy2,3,4

Radiation therapy to chest wall, and regional lymphatics (if not DCIS alone)

Consider systemic therapy2,3,4

Endocrine therapy1

Yes

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1 Consider MD Anderson approved Breast biomarkers
2 See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options
3 See Appendix D - Endocrine Systemic Adjuvant Therapy Options
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NOTE 1:
Breast Cancer — Invasive

Inflammatory Breast Cancer

Stage III¹

- HER2-negative: neoadjuvant doxorubicin and taxane based chemotherapy
- HER2-positive: dual anti-HER2 therapy containing regimen with chemotherapy
- Consider clinical trial(s)

Operable?

Yes

- Multidisciplinary evaluation of response
- Breast surgery with mastectomy and ALND
- Radiation therapy to chest wall and regional lymphatics, if no previous radiation³

No

- Additional systemic therapy² with or without radiation therapy
- Multidisciplinary evaluation of response

Operable?

Yes

- HER2-positive maintenance therapy, see Appendix A

No

- Hormone receptor positive
- Additional systemic therapy²
- Symptom management (supportive care)
- Consider clinical trial(s)

Stage IV¹ (de novo)

- Single/multi-agent systemic therapy
- Symptom management (Supportive care)
- Consider clinical trial(s)

¹ Diagnostic evaluation:
- History and physical
- Obtain photograph to establish baseline clinical appearance and follow up with medical photography for treatment response documentation
- Obtain ultrasound guided core biopsy of the tumor (random biopsies if mass not present); consider skin punch biopsy in addition to breast parenchymal biopsy

² See Appendix A - Neoadjuvant/Adjuvant Chemotherapy Options

³ Evaluate breast and nodes for response to therapy:
- Minimal residual disease or pathologic complete response, age over 45 and negative margins, daily radiation to 66 Gy (2 Gy/fraction, primary fields to 50)
- Significant residual disease, age less than 45 or close or positive margins, twice daily radiation to 66 Gy (1.5 Gy per fraction, primary fields to 51)
APPENDIX A: Neoadjuvant/Adjuvant Chemotherapy Options¹

HER-2 negative disease

Preferred regimens:
- Doxorubicin and cyclophosphamide (AC) either every 3 weeks or every 2 weeks (dose dense) followed or preceded by weekly paclitaxel times 12, or dose dense paclitaxel every 2 weeks
- Fluorouracil, doxorubicin, and cyclophosphamide (FAC) followed or preceded by weekly paclitaxel

Other regimens²:
- Docetaxel and cyclophosphamide (TC)
- Dose-dense doxorubicin and cyclophosphamide (AC) followed or preceded by docetaxel every 3 weeks
- Docetaxel and carboplatin (not routinely used except when there is no response to therapy or patient is borderline operable)

HER-2 positive disease

Optimal duration of adjuvant anti-HER-2 therapy is one year.

All anti-HER2 regimens include trastuzumab every 3 weeks following chemotherapy to complete a full year of trastuzumab including what was given with chemotherapy

Preferred regimens:
- Doxorubicin and cyclophosphamide (AC) followed by paclitaxel plus trastuzumab, AC given every 2 or 3 weeks times 4 cycles and paclitaxel given as dose-dense every 2 weeks times 4 cycles or weekly for 12 cycles
- Docetaxel, carboplatin, trastuzumab (TCH)
- For stage II or higher, consider addition of pertuzumab with chemotherapy portion of regimen or for the entire year with the trastuzumab

Other regimens²:
- Weekly paclitaxel plus trastuzumab (for low-risk disease, such as stage I)
- Consider neratinib extended adjuvant treatment for higher risk (Stage II or higher), given within 1 year following completion of trastuzumab plus or minus pertuzumab maintenance

APPENDIX B: Clinical Scenarios Requiring Individualized Therapy

- Brain metastases
- Ureteral obstruction
- Leptomeningeal disease
- Impending pathologic fracture
- Choroid metastases
- Pathologic fracture
- Extensive local-regional disease
- Pleural effusion
- Cord compression
- Pericardial effusion
- Plexopathy/radiculopathy
- Biliary obstruction
- Superior vena cava syndrome
- Stage IV NED
- Oligometastasis³
- Pregnancy

¹Refer to NCCN Guidelines for specific doses and number of cycles
²May consider other neoadjuvant/adjuvant regimens per NCCN guidelines
³Oligometastases — selected patients with isolated metastatic breast cancer may be considered for definitive treatment

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Refer to NCCN Guidelines for specific doses and number of cycles
May consider other neoadjuvant/adjuvant regimens per NCCN guidelines
Oligometastases — selected patients with isolated metastatic breast cancer may be considered for definitive treatment

APPENDIX B: Clinical Scenarios Requiring Individualized Therapy

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- Oligometastasis³
- Pregnancy

³Oligometastases — selected patients with isolated metastatic breast cancer may be considered for definitive treatment

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Breast Cancer – Invasive
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### APPENDIX C: Recurrent or Metastatic Breast Cancer Chemotherapy Biologic Therapy Treatment Options

#### Preferred single agents:

<table>
<thead>
<tr>
<th>Anthracyclines</th>
<th>Taxanes</th>
<th>Anti-metabolites</th>
<th>Other microtubule inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Paclitaxel</td>
<td>Capecitabine</td>
<td>Vinorelbine</td>
</tr>
<tr>
<td>Pegylated liposomal doxorubicin</td>
<td></td>
<td>Gemcitabine</td>
<td>Eribulin</td>
</tr>
</tbody>
</table>

#### Other single agents:

<table>
<thead>
<tr>
<th>Cyclophosphamide</th>
<th>Docetaxel</th>
<th>Cisplatin</th>
<th>Ixabepilone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Albumin-bound paclitaxel</td>
<td>Epirubicin</td>
<td></td>
</tr>
</tbody>
</table>

#### Combination chemotherapy regimens:

- FAC/CAF (cyclophosphamide, doxorubicin, and fluorouracil)
- FEC (fluorouracil, epirubicin, and cyclophosphamide)
- AC (doxorubicin and cyclophosphamide)
- EC (epirubicin and cyclophosphamide)
- CMF (cyclophosphamide, methotrexate, and fluorouracil)

#### First-line regimens for HER2-positive disease:

- (patients with trastuzumab naïve disease or those who recurred after 6 to 12 months after adjuvant trastuzumab)
- Pertuzumab plus trastuzumab and docetaxel
- Trastuzumab with docetaxel
- Trastuzumab with paclitaxel with or without carboplatin
- Trastuzumab plus pertuzumab (if pertuzumab not previously given)

#### Other options (not considered preferred first options):

- Pertuzumab plus trastuzumab and paclitaxel
- Trastuzumab with vinorelbine
- Trastuzumab with capecitabine

#### Regimens for trastuzumab-exposed HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1) for recurrence (6 to 12 months from adjuvant trastuzumab)
- Lapatinib plus capecitabine
- Trastuzumab plus capecitabine
- Trastuzumab plus pertuzumab
- Trastuzumab plus lapatinib without cytotoxic therapy
- Trastuzumab plus other agent

#### Targeted therapy:

- olaparib for patients with germ line BRCA mutation

---

1After maximal benefit achieved with chemotherapy, consider continuous anti-HER2 therapy alone, if ER or PR positive in combination with appropriate hormonal therapy (does not apply to Ado-trastuzumab emtansine (T-DM1)).
APPENDIX D: Endocrine Systemic Adjuvant Therapy Options

**Premenopausal at diagnosis**:  
1. Tamoxifen for 5 years with or without ovarian suppression or ablation  
2. Ovarian ablation plus aromatase inhibitor for 5 years

**Postmenopausal after initial 5 years?**  
- Yes  
  - Aromatase inhibitor for a minimum of 5 years or  
  - Consider tamoxifen for an additional 5 years (10 years total)
- No  
  - Consider tamoxifen for an additional 5 years (10 years total) or  
  - No further endocrine therapy

**Postmenopausal at diagnosis**:  
1. Aromatase inhibitor an option?  
- Yes  
  - Aromatase inhibitor for at least 5 years or  
  - Tamoxifen for 2-3 years followed by aromatase inhibitor to complete at least 5 years of endocrine therapy or  
  - Tamoxifen for 2-3 years followed by aromatase inhibitor for at least 5 years or  
  - Aromatase inhibitor for 2-3 years followed by tamoxifen to complete at least 5 years of endocrine therapy or  
  - Tamoxifen for 4 ½ to 6 years followed by aromatase inhibitor for at least 5 years or  
  - Tamoxifen for 4 ½ to 6 years, then consider tamoxifen for an additional at least 5 years for a total of 10 years of endocrine therapy  
- No  
  - Tamoxifen for 5 years or  
  - Consider tamoxifen for up to 10 years

**Notes**:  
- Aromatase inhibitors should only be used in patients who are clearly post menopausal [status post surgical bilateral oophorectomy, clinical suppressed on gonadotropin analogues, more that 2 years without clinical menses if stopped early due to chemotherapy, or naturally ceased menses for 1 year (after hysterectomy or less than 55 years old, may want to verify with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels].
- Longer durations of endocrine therapy for greater than 5 years provide larger absolute benefit for higher risk cases (e.g. node-positive, or stage III), although extended aromatase inhibitor greater than 5 years has not yet shown to improve distant metastasis-free or overall survival.
- Bone density should be monitored in postmenopausal patients, consider antiresorptive therapy for osteopenia and institute for osteoporosis. Calcium/Vitamin D replacement recommended for all patients.
- Male patients should be treated similarly to premenopausal patients. Use of aromatase inhibitors or fulvestrant should be accompanied by androgen deprivation therapy (medical/surgical).
- Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy.

**Breast Cancer – Invasive**

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Breast Cancer – Invasive

PRINCIPLES OF BREAST ONCOLOGIC SURGERY

Multidisciplinary management of invasive breast cancer
Surgical management of breast cancer is an important aspect of curative intent therapy. Surgical decision-making is imbedded within the context of the multidisciplinary management of the breast oncology patient (both male and female). Patient participation in clinical trials when appropriate is strongly encouraged.

Diagnosis of breast malignancy
- Dedicated breast imaging at presentation should include bilateral diagnostic mammogram and unilateral breast/nodal basin ultrasound to evaluate extent of disease.
- Consider breast MRI when there is an inability to evaluate extent of disease by conventional imaging or due to breast density and in cases of patients with occult breast primary or Paget’s disease of the nipple with no underlying cancer identified.
- Core needle biopsy is the preferred method of diagnosis of a palpable breast mass or non-palpable breast imaging abnormality. Pathology should include biomarker assessment.
- Excisional biopsy for diagnosis is necessary only in cases of discordance between imaging and core needle biopsy pathology or inability to obtain core needle biopsy.
- Fine needle aspiration biopsy can be used for additional suspicious lesions in the ipsilateral breast to evaluate for multifocal/multi-centric disease and for diagnosis of metastasis in suspicious regional nodes.
- Placement of radio-opaque clip marker with confirmation by imaging should be performed after needle biopsy.
- Medical photography should be utilized in patients who present with skin changes.
- Punch biopsy of the skin should be considered to document skin involvement.

Breast conserving surgery (BCS)
- Breast conserving surgery is appropriate in patients with early stage breast cancer where complete excision of the malignancy may result in an acceptable cosmetic result. Traditionally this has been restricted to patients with unifocal breast tumors. This approach can be considered for selected patients with multifocal/multi-centric malignancy when deemed appropriate by the multidisciplinary team.
- Adjuvant radiation therapy is recommended to decrease the rate of local-regional failure. Contraindication to radiation therapy is a contraindication to BCS.
- Partial breast radiation therapy may be considered in postmenopausal women with ER positive tumors less than or equal to 3 cm and no pathologic nodal involvement.
- “No tumor on ink” is an acceptable margin for invasive breast carcinoma.
- Re-excision segmental mastectomy is recommended in the setting of a positive margin. It should be considered in patients with multiple close margins, discordance between clinical findings and final surgical pathology.
- Imaging guided localization with wire/needle or seed technology is recommended to facilitate intraoperative localization of non-palpable breast lesions.
- Intraoperative specimen radiograph should be performed confirming excision of the lesion, clip marker and localization device and for margin assessment.
- Surgical clips should be placed within the segmental cavity to guide radiation therapy planning.
- Oncoplastic approaches to reconstruction of the segmental mastectomy defect should be offered to patients to facilitate improved aesthetic outcomes.
- New baseline mammogram is recommended at 6 months after the completion of radiation therapy and annually thereafter for breast cancer surveillance.

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Mastectomy
- Immediate post-mastectomy reconstruction should be offered to patients with early stage disease.
- Delayed reconstruction is appropriate in patients with locally advanced or stage III disease. A delayed immediate approach with temporary placement of a tissue expander may be considered after consultation with the plastic surgeon and radiation oncologist.
- Modified radical mastectomy is standard of care in patients with inflammatory breast cancer. Immediate breast reconstruction is contraindicated.
- Nipple sparing mastectomy is oncologically safe and appropriate in high-risk patients undergoing prophylactic mastectomy or patients with early stage disease, appropriate breast anatomy and no evidence of nipple involvement by examination or imaging. Candidacy for nipple sparing approach includes an interdisciplinary discussion with the breast oncologic and reconstructive surgeon.
- Contralateral prophylactic mastectomy may be considered in patients with a high risk for future breast malignancy (including BRCA mutation carrier, strong family history, history of chest wall radiation). This approach should be avoided in patients with locally advanced breast cancer, inflammatory breast cancer and multiple medical co-morbidities which increase risk of perioperative complications. A staged approach to contralateral prophylactic mastectomy at the time of definitive breast reconstruction is preferred in patients with advanced disease.

Surgical staging of the axilla
- Axillary ultrasound and physical examination are recommended for clinical axillary staging in invasive breast cancer. Biopsy of suspicious axillary node(s) and placement of radio-opaque clip marker if positive for metastasis is recommended.
- Sentinel node dissection is the standard of care for axillary staging in patients with clinically node negative breast cancer. Surgeons should demonstrate proficiency in lymphatic mapping through residency/fellowship training and/or a minimum of 20 cases with an identification rate of greater than 85% and a false negative rate of less than 5%. After neoadjuvant chemotherapy, dual tracer technique utilizing blue dye and technetium radioisotope is recommended to improve sentinel node identification and to reduce the chance of a false negative sentinel node.
- Targeted axillary dissection (TAD) is appropriate surgical staging in selected patients with clinically node positive breast cancer treated with neoadjuvant systemic therapy to evaluate for residual nodal disease after discussion with the multidisciplinary team. TAD includes sentinel node dissection using dual tracer technique and excision of the biopsy proven clipped axillary node via radiographic localization.
Management of biopsy proven axillary disease

- Axillary lymph node dissection (level I and II) is indicated in patients with biopsy proven clinically node positive disease and pathologic positive nodal involvement. Level III dissection may be considered in patients with level III residual disease after neoadjuvant chemotherapy.
- Axillary dissection may be omitted in
  - Patients undergoing breast conserving surgery for early stage clinically node negative (T1 and T2 N0 M0) breast cancer and 1-2 positive sentinel nodes planned for adjuvant radiation therapy and adjuvant systemic therapy.
  - Patients treated with neoadjuvant chemotherapy with cT1 or T2 N1 (less than 4 suspicious or involved nodes at presentation) disease and appropriate response to therapy determined by normal axillary physical exam and resolution of findings on axillary ultrasound who undergo targeted axillary dissection (TAD) showing no residual nodal disease (including isolated tumor cells). Radiation therapy is recommended in the omission of axillary dissection and preoperative multidisciplinary discussion is required.
- Evaluation by a physical therapist should be considered in patients undergoing axillary lymph node dissection for improved range of motion and screening for lymphedema.

Neoadjuvant systemic therapy

- Neoadjuvant systemic therapy is standard of care in patients with inflammatory breast cancer, locally advanced breast cancer and occult primary with axillary metastasis.
- In early stage operable breast cancer, neoadjuvant systemic therapy should be considered in patients planned for adjuvant chemotherapy including those triple negative receptor status, HER2-positive and/or biopsy proven node positive disease.
- Neoadjuvant chemotherapy is also indicated in patients who desire breast conservation and are not candidates based on tumor size to breast volume ratio.
- Neoadjuvant endocrine therapy may be considered in selected cases of ER positive breast cancer in postmenopausal women.
- Extent of disease in the breast and regional nodes should be determined and documented prior to initiation of neoadjuvant systemic therapy.

Management of local-regional recurrence

- Breast imaging including mammogram (if recurrence after BCS), breast/chest wall and nodal basin ultrasound and MRI when appropriate should be obtained.
- Diagnosis by core needle biopsy including biomarker evaluation is recommended.
- Staging should be performed to evaluate for distant metastatic disease.
- Multimodality therapy is recommended including systemic therapy and radiation therapy if possible. If resectable at diagnosis may proceed with local-regional management followed by adjuvant systemic therapy. Neoadjuvant systemic therapy may also be considered.
- Surgical management of in-breast tumor recurrence after previous radiotherapy should include total mastectomy. Breast conserving surgery may be considered if no prior radiotherapy or if re-irradiation is possible.
- Surgical management of chest wall recurrence after mastectomy should include wide local excision of the chest wall recurrence.
- R0 resection with negative margins is critical and en-bloc resection of underlying musculature or chest wall may be necessary with chest wall coverage/reconstruction.
- Consider sentinel node staging in the setting of in-breast tumor recurrence in patients without previous axillary dissection.

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PRINCIPLES OF BREAST ONCOLOGIC SURGERY

Stage IV disease
- Traditionally, surgical management of the primary and axilla are not recommended in the setting of stage IV disease.
- In selected patients with oligometastatic disease, excellent response to systemic therapy and acceptable performance status, surgery of the primary tumor and nodal involvement may be considered to achieve no evidence of disease (NED) status. Definitive management of the oligo metastatic site(s) is also recommended.

Management of patients at high-risk for breast malignancy
- Patients with hereditary breast and ovarian cancer syndrome, deleterious BRCA1 and 2 mutations, history of chest wall radiation therapy and greater than 20% lifetime risk of breast cancer should be considered for high-risk screening. High-risk screening includes bi-annual clinical examination and bilateral mammogram and MRI alternating every 6 months.
- Consideration for prophylactic mastectomy for risk reduction may be appropriate in this population. Referral to plastic surgery for reconstruction is recommended. Psychosocial and body image concerns should be addressed prior to surgery.

Special considerations
- Omission of breast and/or axillary surgery may be appropriate in patients with advanced age, multiple medical co-morbidities and other clinical competing morbidity/mortality risks in comparison to the breast malignancy.
- Palliative mastectomy may be considered in patients with advanced local progression, symptomatic fungating and/or bleeding tumors not responsive to systemic therapy.


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SUGGESTED READINGS - continued


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**SUGGESTED READINGS - continued**


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*SUGGESTED READINGS - continued*
SUGGESTED READINGS - continued


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Department of Clinical Effectiveness V15
Approved by Executive Committee of the Medical Staff on 02/27/2018

Breast Cancer – Invasive

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SUGGESTED READINGS – Chemotherapy Regimens for Metastatic Breast Cancer and in Combination with Transtuzumab


This practice consensus algorithm is based on majority expert opinion of the Breast Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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