Breast Cancer – Invasive Stage I-III

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TABLE OF CONTENTS

- Initial Evaluation.................................................................Page 2
- Hormone receptor-positive/HER2-negative.............................................Page 3
- Hormone receptor-positive/HER2-positive or Hormone receptor-negative/HER2-positive................................................Page 4
- Hormone receptor-negative/HER2-negative (triple negative breast cancer)........................................................Page 5
- Evaluation During and Post Neoadjuvant Treatment..........................Page 6
- Radiation Therapy ......................................................................Page 7
- Surveillance..................................................................................Page 8
- Evaluation for Local Recurrence.......................................................Page 9
- Appendix A: Genomic Considerations for Determination of Prognosis and Need for Adjuvant Chemotherapy in Patients with HR+ Breast Cancer........................................................................Page 10
- Appendix B: Neoadjuvant/Adjuvant Systemic Therapy Options........Page 11
- Appendix C: Endocrine Systemic Neoadjuvant/Adjuvant Therapy Options..........................................................Page 12
- Appendix D: Selection of Patients for Radiation to Regional Lymphatics.................................................................Page 13
- Appendix E: Recurrent Systemic Therapy Treatment Options ..........Page 14
- Principles of Breast Oncologic Surgery ..............................................Pages 15-17
- Suggested Readings.......................................................................Pages 18-22
- Development Credits......................................................................Pages 23-24

1 There are special circumstances in which these guidelines do not apply. These include, but are not limited to:
- Sarcoma of the breast
- Lymphoma of the breast
- Patients with lupus and scleroderma
- Patients with limited life expectancy
- Cancer during pregnancy
- Special histologies (i.e., tubular, medullary, pure papillary, or colloid)

2 For inflammatory breast cancer, see Breast Cancer – Inflammatory (IBC) algorithm
**Breast Cancer – Invasive Stage I-III**

**INITIAL MULTIDISCIPLINARY EVALUATION**

- History and physical
- Pathology review
- Diagnostic imaging (bilateral mammography and ultrasound) of breast and regional nodal basins with FNA or core biopsy of suspicious nodes
- Clip placed in largest node with biopsy confirmed metastasis
- CBC with differential, liver function tests (total bilirubin, alkaline phosphatase, transaminases), creatinine
- Genetic testing and counseling as indicated
- Lifestyle risk assessment

<table>
<thead>
<tr>
<th>HR-positive/HER2-negative</th>
<th>HR-positive/HER2-positive</th>
<th>HR-negative/HER2-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 (human epidermal growth factor receptor) status</td>
<td>ER, PR status</td>
<td>Histologic type</td>
</tr>
<tr>
<td>Stage I</td>
<td>Consider Ki-67</td>
<td>Consider Ki-67</td>
</tr>
<tr>
<td>Clinical/imaging tumor size</td>
<td>Lymph node status</td>
<td>Body imaging as indicated</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Lymph node status</td>
<td>Body imaging as indicated</td>
</tr>
</tbody>
</table>

**TREATMENT**

- Favorable characteristics (grade I/II, strongly ER/PR positive, low Ki-67)
- For adverse features (large nodal burden, high Ki-67, high grade)

**Definitive breast and nodal surgery (see Page 3)**

**If unfavorable breast to tumor size ratio and patient desires BCT, consider neoadjuvant endocrine therapy**

**Definitive surgery and sentinel lymph node biopsy (see Page 4)**

**Definitive surgery and sentinel lymph node biopsy (see Page 4)**

**Definitive surgery and sentinel lymph node biopsy (see Page 4)**

**Definitive surgery and sentinel lymph node biopsy (see Page 5)**

**Definitive surgery and sentinel lymph node biopsy (see Page 5)**

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**Definitive surgery and sentinel lymph node biopsy (see Page 5)**

**Definitive surgery and sentinel lymph node biopsy (see Page 5)**

- BCT = breast conservation therapy
- ER = estrogen receptor
- FNA = fine needle aspiration
- HR = hormone receptor
- PR = progesterone receptor

**Note**: Consider Clinical Trials as treatment options for eligible patients.

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Department of Clinical Effectiveness V16

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Breast Cancer – Invasive Stage I-III

**SURGICAL CONSIDERATIONS**

- **BCT** with axillary surgery or Total mastectomy with axillary lymph node surgery with or without reconstruction
- Total mastectomy with SLN surgery with or without reconstruction
- Consider neoadjuvant endocrine therapy, if patient is interested in BCT (see Appendix C)
- See Page 6 for evaluation during and upon completion of chemotherapy

**TREATMENT**

- Consider genomic testing for risk stratification to guide chemotherapy (see Appendix A for genomic testing and indications for chemotherapy)
- See Appendix B and Appendix C for treatment options, if indicated
- See Pathologically node negative
- Consider g
- Consider neoadjuvant chemotherapy
- Adjuvant chemotherapy (see Appendix B) followed by adjuvant endocrine therapy (see Appendix C)
- See Page 7 for radiation therapy
- Total mastectomy with or without Neoadjuvant Chemotherapy for guidance on completion of ALND
- Refer to Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy for guidance on completion of ALND

**Favorable characteristics** (grade I/II, strongly ER/PR positive, low Ki-67)

- Candidate for **BCT** at presentation?
  - Yes
  - No
  - Pathologically node negative
  - Pathologically node positive
  - No further axillary surgery
  - Meets Z0011 criteria?
  - Yes
  - No

**Tumor to breast size ratio** allows for acceptable cosmetic result

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

1. Patients with hereditary breast and ovarian cancer syndrome, deleterious BRCA1 and 2 mutations, history of chest wall radiation therapy and > 20% lifetime risk of breast cancer should be considered for risk reducing mastectomy
2. Candidates for BCT: ● Tumor to breast size ratio allows for acceptable cosmetic result ● No evidence of diffuse calcifications on mammogram
3. 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 dissection with selective localization and removal of clipped node.
4. For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is generally preferred. Pre-operative consultation with Plastic Surgery and Radiation Oncology recommended.
5. Genomic testing may not be indicated for post-surgery patients with all favorable prognostic factors present
6. 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) and are planned for whole breast irradiation and systemic therapy
7. Surgeries with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of > 85% and a false negative rate of < 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. Definitive surgery should be considered if contraindications to systemic therapy

**Note:** Consider Clinical Trials as treatment options for eligible patients.
SURGICAL CONSIDERATIONS

HR-positive/HER2-positive with tumor < 2 cm or HR-negative/HER2-positive with tumor < 1 cm and clinically node negative
- Candidate for BCT at presentation?
  - Yes
    - BCT with axillary surgery
    - Total mastectomy with axillary lymph node surgery with or without reconstruction
  - No
    - Total mastectomy with SLN surgery with or without reconstruction
    - Consider neoadjuvant systemic therapy, if patient is interested in BCT (see Appendix B)

HR-positive/HER2-positive with tumor ≥ 2 cm or HR-negative/HER2-positive with tumor ≥ 1 cm with any lymph node status
- Neoadjuvant chemotherapy and anti-HER2 therapy (see Appendix B) followed by definitive surgery
- See Page 6 for evaluation during and on completion of systemic therapy

ALND = axillary lymph node dissection
BCT = breast conservation therapy
HR = hormone receptor
SLN = sentinel lymph node

1. Patients with hereditary breast and ovarian cancer syndrome, deleterious BRCA1 and 2 mutations, history of chest wall radiation therapy and > 20% lifetime risk of breast cancer should be considered for risk reducing mastectomy
2. Candidates for BCT: ● Tumor to breast size ratio allows for acceptable cosmetic result ● No evidence of diffuse calcifications on mammogram
3. Candidates for limited axillary surgery with a prior biopsy proven axillary lymph node metastasis must have documented removal of the prior biopsy and clipped lymph node. Preferred approach is targeted axillary dissection which includes SLN dissection with selective localization and removal of clipped node.
4. For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is generally preferred. Pre-operative consultation with Plastic Surgery and Radiation Oncology recommended.
5. 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) and are planned for whole breast irradiation and systemic therapy
6. Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of > 85% and a false negative rate of < 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
7. Definitive surgery should be considered if contraindications to systemic therapy

TREATMENT BASED ON PATHOLOGIC FINDINGS

Pathologically node negative
- Meets Z0011 criteria
  - Yes
    - No further axillary surgery
  - No
    - Refer to Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy for guidance on completion of ALND

Pathologically node positive
- Residual disease?
  - Yes
    - T-DM1 (ado-trastuzumab emtansine) for the remainder of one year and endocrine therapy as indicated (see Appendix C)
  - No
    - Anti-HER2 antibody therapy alone to complete one-year of therapy and endocrine therapy as indicated (see Appendix C)
SURGICAL CONSIDERATIONS

<table>
<thead>
<tr>
<th>Tumor &lt; 1 cm and lymph nodes negative</th>
<th>Candidate for BCT at presentation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-negative/HER2-negative (triple negative breast cancer)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Pathologically node negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BCT with axillary surgery or Total mastectomy with axillary lymph node surgery with or without reconstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor ≥ 1 cm with any lymph node status</th>
</tr>
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</table>

| Total mastectomy with SLN surgery with or without reconstruction |

<table>
<thead>
<tr>
<th>Pathologically node positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meets Z0011 criteria?</td>
</tr>
</tbody>
</table>

| • Neoadjuvant chemotherapy (see Appendix B) followed by definitive surgery |
| • See Page 6 for evaluation during and on completion of chemotherapy |

TREATMENT BASED ON PATHOLOGIC FINDINGS

<table>
<thead>
<tr>
<th>Pathologically node negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider adjuvant chemotherapy (see Appendix B)</td>
</tr>
<tr>
<td>• See Page 7 for radiation therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No further axillary surgery</th>
</tr>
</thead>
</table>

| Refer to Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy for guidance on completion of ALND |
| • Adjuvant chemotherapy (see Appendix B) |
| • See Page 7 for radiation therapy |

ALND = axillary lymph node dissection  BCT = breast conservation therapy  HR = hormone receptor  SLN = sentinel lymph node

1 Patients with hereditary breast and ovarian cancer syndrome, deleterious BRCA1 and 2 mutations, history of chest wall radiation therapy and > 20% lifetime risk of breast cancer should be considered for risk reducing mastectomy

2 Candidates for BCT: • Tumor to breast size ratio allows for acceptable cosmetic result • No evidence of diffuse calcifications on mammogram

3 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 dissection with selective localization and removal of clipped node.

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

5 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) and are planned for whole breast irradiation and systemic therapy

6 Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of > 85% and a false negative rate of < 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

7 Definitive surgery should be considered if contraindications to systemic therapy

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Breast Cancer – Invasive Stage I-III

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Note: Consider Clinical Trials as treatment options for eligible patients.

EVALUATION DURING AND POST NEOADJUVANT TREATMENT

Patients receiving neoadjuvant systemic therapy

• 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 systemic therapy if unresectable, and then follow local treatment guidelines and systemic adjuvant therapy guidelines

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

BCT = breast conservation therapy
SLN = sentinel lymph node

1 Neoadjuvant response assessment with MRI in cases where mammogram and/or ultrasound are insufficient
2 Candidates for BCT:
• Tumor to breast size ratio allows for acceptable cosmetic result
• No evidence of diffuse calcifications on mammogram
• Negative margins after surgery
• Resolution of any skin edema after systemic therapy
3 Surgeons with an established record of lymphatic mapping experience for breast cancer (a minimum of 20 cases with an identification rate of > 85% and a false negative rate of < 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
4 Limited nodal involvement at presentation is defined as ≤ 3 abnormal nodes on axillary ultrasound. The largest biopsy proven positive node should be clipped at presentation and documentation of clipped nodes is required at surgery.
5 For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is preferred.

See Appendix B and C for adjuvant systemic therapy based on tumor subtype
See Page 7 for radiation therapy

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**Breast Cancer – Invasive Stage I-III**

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### RADIATION THERAPY

- T1-2 with negative lymph node(s)
  - For patients with BCT, radiation to breast and refer to Appendix D for decision on regional lymphatics

- T1-2 with 1-3 positive lymph node(s)
  - For patients with mastectomy, refer to Appendix D for decision on regional lymphatics and chest wall for patients with mastectomy or no radiation

- T3 or ≥4 involved lymph nodes
  - Post mastectomy radiation therapy to chest wall and regional lymphatics
  - Whole breast radiation therapy1 with regional lymphatics for BCT

- Recurrent disease no prior radiation
  - Post mastectomy radiation therapy to chest wall and regional lymphatics

1 Radiation therapy for BCT and post-mastectomy radiation are generally delivered at completion of chemotherapy. For early stage node negative patients, patients waiting for genomic scores, or patients eligible for partial breast irradiation, radiation therapy may be delivered before chemotherapy.

2 See Appendix D: Selection of Patients for Radiation to Regional Lymphatics

### TREATMENT

- Whole breast radiation therapy
  - Dose:
    - 4,005 cGy in 15 fraction plus or minus 1,000-1,600 cGy boost in 5-8 fractions, depending on margin. Consider omission of boost if low grade, older age, or hormone positive.
    - Low risk patients age > 50 years and hormone positive, consider 2,600 cGy in 5 fractions delivered daily for 5 days
  - Partial breast radiation, if low risk patients age > 50 years and hormone positive
    - Dose:
      - 3,850 cGy in 10 fractions delivered twice daily

- Whole breast and level I/II axilla
  - Dose:
    - 4,005 cGy in 15 fractions plus or minus 1,000-1,600 cGy boost in 5-8 fractions, depending on margin. Consider for low risk node positive patients with nomogram predicting low risk of additional nodes

- Whole breast or chest wall and undissected draining lymphatics, to include internal mammary nodes (IMN), supraclavicular (SCV), and level III axilla
  - Include level I/II axilla if ALND not performed
  - Dose:
    - 5,000 cGy in 25 fractions plus 1,000-1,600 cGy boost in 5-8 fractions, depending on margin
    - 1,000-1,600 cGy boost in 5-8 fractions to involved unresected nodes

- Chest wall and undissected draining lymphatics
  - Dose:
    - 5,400 cGy in 27 fractions plus 1,200 cGy boost in 6 fractions
**SURVEILLANCE**

- Physical exam at least every 3-6 months for 5 years, then annually after year 5
- If breast conservation therapy (BCT), mammogram of treated breast at 6 months following completion of radiation therapy, then annually
- For patients with germline mutations, alternating mammogram and breast MRI every 6 months; consider annual breast MRI depending on age and breast density as indicated
- 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

See Page 9 for Evaluation for Local Recurrence
Note: Consider Clinical Trials as treatment options for eligible patients.

EVALUATION FOR LOCAL RECURRENCE

Ipsilateral breast/chest wall recurrence or ipsilateral regional nodal recurrence

- Systemic workup including biopsy to confirm recurrence and evaluate presence of distant metastasis:
  - Biomarkers\(^1\) of breast/chest wall recurrence or nodal recurrence (if no breast/chest wall recurrence)
  - If intact breast, bilateral diagnostic mammogram
  - Ultrasound of affected breast including regional nodal basins
  - Body imaging for invasive recurrence
  - Multidisciplinary team discussion to determine appropriate sequencing of treatment options

  \[\text{Yes} \quad \text{Local only recurrence} \quad \text{See NCCN guidelines}\]

  \[\text{No} \quad \text{Distant metastasis}\]^2

  \[\text{Regional only or local and regional recurrence} \quad \text{Axillary recurrence} \quad \text{Supraclavicular recurrence} \quad \text{Internal mammary node recurrence} \]

TREATMENT FOR RECURRENCE

Initial treatment with lumpectomy plus radiation therapy

Total mastectomy plus axillary lymph node staging if level I/II axillary dissection not previously done\(^2\)

Initial treatment with mastectomy plus level I/II axillary dissection and prior radiation therapy

Surgical resection if possible\(^2\)

Initial treatment with mastectomy and no prior radiation therapy\(^2\)

Surgical resection if possible plus radiation therapy\(^3\)

Axillary recurrence

- Surgical resection if possible plus radiation therapy\(^2\) if possible
- Consider preoperative systemic therapy, as per tumor subtype

Supraclavicular recurrence

- Radiation therapy\(^2,3\) if possible
- Consider systemic therapy, as per tumor subtype, prior to radiation therapy

Internal mammary node recurrence

- Radiation therapy\(^2,3\) if possible
- Consider systemic therapy, as per tumor subtype, prior to radiation therapy

Consider systemic therapy:
- See Appendix B for preoperative/adjuvant chemotherapy plus/minus anti-HER2 therapy
- See Appendix C for adjuvant endocrine therapy
- See Appendix E for recurrent systemic therapy treatment options

\(^1\) Consider MD Anderson approved breast biomarkers

\(^2\) Consider referral to radiation therapy for evaluation of re-irradiation if prior treatment > 2 years and for potential clinical benefit

\(^3\) See Page 7 for radiation therapy

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APPENDIX A: Genomic Considerations for Determination of Prognosis and Need for Adjuvant Chemotherapy in Patients with HR+ Breast Cancer

Genomic panels supported by level 1 or 2 evidence:
- 21-gene recurrence score (Oncotype DX®)
- 12-gene risk score (EndoPredict®)
- PAM50 risk of recurrence (ROR) score (Prosigna™ Breast Cancer Prognostic Gene Signature Assay)
- Breast Cancer Index

<table>
<thead>
<tr>
<th>Genomic Assay</th>
<th>Benefit from Chemotherapy¹</th>
<th>No Benefit from Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX® recurrence score (RS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Age ≤ 50</td>
<td>RS ≥ 16</td>
<td>RS &lt; 16</td>
</tr>
<tr>
<td>○ Age &gt; 50</td>
<td>RS &gt; 25</td>
<td>RS ≤ 25</td>
</tr>
<tr>
<td>EndoPredict® risk score (RS)</td>
<td>RS &gt; 3.3287 (high)</td>
<td>RS &lt; 3.3287 (low)</td>
</tr>
<tr>
<td>Prosigna™ recurrence score (RS)</td>
<td>RS ≥ 41</td>
<td>RS &lt; 41</td>
</tr>
<tr>
<td>Breast Cancer Index recurrence score (RS)</td>
<td>RS ≥ 5</td>
<td>RS &lt; 5</td>
</tr>
</tbody>
</table>

¹These assays have been validated for use in patients with negative lymph nodes. Evidence in patients with positive lymph nodes is emerging, but is not yet compelling.

APPENDIX B: Chemotherapy and Anti-HER2 Neoadjuvant/Adjuvant Systemic Therapy Options

### HER2-negative disease

**Preferred regimens:**
- AC-T (doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV either every 3 weeks or every 2 weeks (dose-dense) followed or preceded by weekly paclitaxel 80 mg/m² for 12 doses, or dose-dense paclitaxel every 2 weeks)
- FAC-T (fluorouracil 500 mg/m² IV on Day 1 and 8, doxorubicin 50 mg/m² IV on Day 1, and cyclophosphamide 500 mg/m² IV on Day 1 followed or preceded by weekly paclitaxel 80 mg/m²)
- Consider the addition of carboplatin (AUC 6 IV) for triple negative disease
- TC (docetaxel 75 mg/m² IV on Day 1 and cyclophosphamide 600 mg/m² IV on Day 1) every 3 weeks

**Other regimens:**
- Dose-dense AC (doxorubicin and cyclophosphamide) 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)

### HER2-positive disease

Optimal duration of adjuvant anti-HER2 antibody 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:**
- AC-T (doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV followed by paclitaxel 80 mg/m² IV plus trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg IV, plus pertuzumab 840 mg IV followed by 420 mg IV), AC (doxorubicin and cyclophosphamide) given every 2 or 3 weeks for 4 cycles and dose-dense paclitaxel every 2 weeks for 4 cycles or weekly for 12 cycles
- TCHP (docetaxel 75 mg/m² IV, carboplatin AUC 6 IV, trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg IV, pertuzumab 840 mg IV followed by 420 mg IV)
- For stage II or higher, consider addition of pertuzumab with chemotherapy portion of regimen or for the entire year with the trastuzumab

**Other regimens:**
- Weekly paclitaxel plus trastuzumab (for low-risk disease, such as stage I)
- T-DM1 adjuvant therapy after preoperative trastuzumab for residual HER2 positive disease
- Consider use of neratinib after completion of T-DM1 therapy for patients with high risk tumors (multiple positive nodes, locally advanced disease, etc.)

T-DM1 = ado-trastuzumab emtansine

1. Refer to NCCN Guidelines for specific doses and number of cycles
2. May consider other neoadjuvant/adjuvant regimens per NCCN guidelines
## APPENDIX C: Endocrine Neoadjuvant/Adjuvant Therapy Options

<table>
<thead>
<tr>
<th>First Line Therapy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal</strong></td>
<td><strong>Premenopausal</strong></td>
</tr>
<tr>
<td>○ OFS plus AI&lt;sup&gt;1&lt;/sup&gt; for 5 years</td>
<td>○ OFS plus tamoxifen for patients who cannot tolerate AI</td>
</tr>
<tr>
<td>○ Tamoxifen for 5-10 years</td>
<td>○ Consider adjuvant bisphosphonate for postmenopausal women</td>
</tr>
<tr>
<td><strong>Postmenopausal</strong> at diagnosis</td>
<td><strong>Postmenopausal</strong></td>
</tr>
<tr>
<td>○ AI&lt;sup&gt;2,3&lt;/sup&gt; for 5-7 years (maximum of 10 years)</td>
<td>○ Consider OFS plus tamoxifen for patients who cannot tolerate AI</td>
</tr>
<tr>
<td>○ Tamoxifen for 5-10 years only if AI&lt;sup&gt;1&lt;/sup&gt; not possible</td>
<td></td>
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</table>

### Notes:

- Longer durations of endocrine therapy for > 5 years provide larger absolute benefit for higher risk cases (e.g., node-positive, or stage III), although extended aromatase inhibitor > 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 is recommended for all patients.

1. Male patients should be treated similarly to premenopausal patients. Use of aromatase inhibitors or fulvestrant should be accompanied by androgen deprivation therapy (medical/surgical).
2. Aromatase inhibitors should only be used in patients who are clearly postmenopausal (status post surgical bilateral oophorectomy, clinically suppressed on gonadotropin analogues, > 2 years without clinical menses if stopped early due to chemotherapy, or naturally ceased menses for 1 year; for patients after hysterectomy or < 55 years old, consider verifying with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels)
3. Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy
APPENDIX D: Selection of Patients for Radiation to Regional Lymphatics

<table>
<thead>
<tr>
<th>pN1 (macromets, &gt; 2 mm):</th>
<th>pN0, pN0(i+) or micromets:</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Age ≤ 40 years, upfront surgery</td>
<td>● Meets at least 3 of the following criteria:</td>
</tr>
<tr>
<td>● 3+ LNs, upfront surgery</td>
<td>○ T3</td>
</tr>
<tr>
<td>● ypN+</td>
<td>○ N1(mic)</td>
</tr>
<tr>
<td>● cT3 N1</td>
<td>○ Multiple mic nodes</td>
</tr>
<tr>
<td>● ER negative, upfront surgery</td>
<td>○ Medial tumor location</td>
</tr>
<tr>
<td>● Age &lt; 50 years with recurrence score &gt; 18, if known</td>
<td>○ Age ≤ 45 years</td>
</tr>
<tr>
<td>● SLNB only and &gt; 33% risk of additional nSLNS</td>
<td>○ Grade 3</td>
</tr>
<tr>
<td>● Age &gt; 40 years, p1-2LN+, ER positive and meets at least two of the following criteria:</td>
<td>○ LVSI</td>
</tr>
<tr>
<td>○ Luminal B (Ki-67 &gt; 20% or HER2 positive)</td>
<td>○ ER negative</td>
</tr>
<tr>
<td>○ Grade 3</td>
<td>○ Luminal B (high Ki-67 &gt; 20% or HER2 positive)</td>
</tr>
<tr>
<td>○ Lymphovascular space invasion (LVSI)</td>
<td>○ SLN only, &gt; 33% nomogram risk</td>
</tr>
<tr>
<td>○ High genomic score</td>
<td>○ High genomic score</td>
</tr>
<tr>
<td>○ Medial tumor location</td>
<td></td>
</tr>
</tbody>
</table>
### Preferred single agents:

**Anthracyclines**
- Doxorubicin
- Pegylated liposomal doxorubicin

**Taxanes**
- Paclitaxel

**Anti-metabolites**
- Capecitabine
- Gemcitabine

**Other microtubule inhibitors**
- Vinorelbine
- Eribulin

### Other single agents:
- Cyclophosphamide
- Docetaxel
- Cisplatin
- Carboplatin
- Ixabepilone
- Albumin-bound paclitaxel
- Epirubicin
- Sacituzumab govitecan
- Mitomycin C

### Combination chemotherapy regimens:
- FAC/CAF (cyclophosphamide, doxorubicin, and fluorouracil)
- EC (epirubicin and cyclophosphamide)
- AC (doxorubicin and cyclophosphamide)
- FEC (fluorouracil, epirubicin, and cyclophosphamide)
- Docetaxel and capecitabine
- CMF (cyclophosphamide, methotrexate, and fluorouracil)
- Gemcitabine and carboplatin
- Ixabepilone/capecitabine

### HER2 Based Therapies

#### First-line regimens for HER2-positive disease
- Pertuzumab plus trastuzumab and docetaxel
- Pertuzumab plus trastuzumab and paclitaxel

#### Other options (not considered preferred first options):
- Trastuzumab with docetaxel
- Trastuzumab with paclitaxel with or without carboplatin
- Trastuzumab with vinorelbine
- Trastuzumab with capecitabine
- Trastuzumab plus pertuzumab (if pertuzumab not previously given)

#### Regimens for trastuzumab-exposed HER2-positive disease
- T-DM1 (ado-trastuzumab emtansine) for recurrence (6 to 12 months from adjuvant trastuzumab)
- Trastuzumab plus lapatinib without cytotoxic therapy
- Fam-trastuzumab deruxtecan-nxki

#### BRCA-positive directed therapies: Olaparib or talazoparib

### Endocrine based therapies

**Aromatase inhibitors (AI)**
- Anastrozole
- Letrozole
- Exemestane
- AI with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
- Exemestane plus everolimus

**Fulvestrant**
- Fulvestrant with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
- Fulvestrant with alpelisib
- Fulvestrant with AI

**Tamoxifen**
- Abemaciclib single agent
- Megestrol acetate

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1 After maximal benefit achieved with chemotherapy, consider continuous anti-HER2 therapy alone, if ER or PR positive, in combination with appropriate endocrine therapy (does not apply to T-DM1).
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 embedded 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 in the breast and regional nodes.
- Consider MRI breast 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/m multicentric disease and for diagnosis of metastasis in suspicious regional nodes.
- Placement of radio-opaque clip marker with confirmation by imaging should be performed at the time of 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. Recommend multidisciplinary team discussion prior to surgical treatment.
- Partial breast radiation therapy may be considered in postmenopausal women with ER positive tumors ≤ 3 cm and no pathologic nodal involvement.
- “No ink on tumor” 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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PRINCIPLES OF BREAST ONCOLOGIC SURGERY - continued

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 at the initial surgery 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 risk-reducing 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 risk-reducing 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 comorbidities which increase risk of perioperative complications. A staged approach to contralateral risk-reducing 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 (usually placed in the largest node with documentation of the number of abnormal nodes).
- 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 > 85% and a false negative rate of < 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 following systemic therapy 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 image-guided 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 who are not Z0011 candidates or those who have pathologic positive nodal involvement following systemic therapy. Level III dissection may be considered in patients with residual level III disease after neoadjuvant chemotherapy. Radiation therapy can be considered as an alternative in selected patients.
- Axillary dissection may be omitted in
  - Patients undergoing breast conserving surgery for early stage clinically node negative (T1 and T2 N0 M0) breast cancer or 1-2 positive sentinel nodes planned for adjuvant whole breast radiation therapy and adjuvant systemic therapy
  - Patients treated with neoadjuvant chemotherapy with cT1 or T2 N1 (fewer 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 TAD showing no residual nodal disease (including isolated tumor cells). Axillary radiation therapy is recommended in the omission of axillary dissection, and preoperative multidisciplinary discussion is required.
- Evaluation by a physical therapist should be performed in patients undergoing axillary lymph node dissection for improved range of motion and screening for lymphedema

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Neoadjuvant systemic therapy
- Neoadjuvant systemic therapy is standard practice 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 with triple receptor negative disease (TNBC), HER2-positive disease and/or biopsy proven node-positive disease
- Neoadjuvant chemotherapy can also be considered 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-negative disease
- 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
- Multidisciplinary team discussion should occur to determine appropriate sequencing of treatment options
- 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 should be considered especially for HER2-positive and triple negative breast cancer (TNBC).
- 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. Lymphoscintigraphy can be helpful to identify extra-axillary drainage.

Stage IV disease
- Traditionally, surgical management of the primary and regional nodes 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 oligometastatic 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 risk-reducing 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
- Radiation therapy or palliative mastectomy may be considered in patients with advanced local progression, symptomatic fungating and/or bleeding tumors not responsive to systemic therapy.
SUGGESTED READINGS


Continued on next page
Breast Cancer – Invasive Stage I-III


SUGGESTED READINGS - continued
SUGGESTED READINGS - continued


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SUGGESTED READINGS - continued


Sharma, R., Bedrosian, I., Lucci, A., Hwang, R., Rouke, L., Qiao, W., … Kuerer, H. (2010). Present-day locoregional control in patients with T1 or T2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. *Annals of Surgical Oncology*, 17(11), 2899–2908. https://doi.org/10.1246/sao.1010-1089-x


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SUGGESTED READINGS - continued


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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.
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