Breast Cancer – Invasive[1] Stage I-III[2]

TABLE OF CONTENTS

[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

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

INITIAL MULTIDISCIPLINARY EVALUATION

- History and physical
- Pathology review[1]
- 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[2]
- Lifestyle risk assessment[3]

CLINICAL STAGING

- HER2 (human epidermal growth factor receptor) status
- ER, PR status
- Histologic type
- Composite histologic grade
- Consider *Ki-67*
- Clinical/imaging tumor size
- Lymph node status
- Body imaging as indicated[4]

TREATMENT

HR-positive/ HER2-negative

- Favorable characteristics (grade I/II, strongly ER/PR positive, low *Ki*-67) → • Definitive breast and nodal surgery (see Page 3) • If unfavorable breast to tumor size ratio and patient desires BCT[5], consider neoadjuvant endocrine therapy
- For adverse features (large nodal burden, high *Ki*-67, high grade) → Consider neoadjuvant chemotherapy (see Page 3)

HR-positive/ HER2-positive

- Tumor < 2 cm and lymph nodes negative → Definitive surgery and sentinel lymph node biopsy (see Page 4)
- Tumor ≥ 2 cm with any lymph node status → Neoadjuvant systemic therapy (see Page 4)

HR-negative/ HER2-positive

- Tumor < 1 cm and lymph nodes negative → Definitive surgery and sentinel lymph node biopsy (see Page 4)
- Tumor ≥ 1 cm with any lymph node status → Neoadjuvant anti-HER2 and chemotherapy (see Page 4)

HR-negative/ HER2-negative (triple negative breast cancer)

- Tumor < 1 cm and lymph nodes negative → Definitive surgery and sentinel lymph node biopsy (see Page 5)
- Tumor ≥ 1 cm with any lymph node status → Neoadjuvant chemotherapy (see Page 5)

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

[1] Review MD Anderson approved breast biomarkers
[2] See Genetic Counseling algorithm
[3] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[4] Patients with signs or symptoms suggestive of metastatic disease should be considered for additional imaging
[5] Candidates for BCT: • Tumor to breast size ratio allows for acceptable cosmetic result • No evidence of diffuse calcifications on mammogram

Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

Breast Cancer – Invasive Stage I-III

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

SURGICAL CONSIDERATIONS[1]

HR-positive/ HER2-negative

- Favorable characteristics (grade I/II, strongly ER/PR positive, low *Ki-67*)
  - Candidate for BCT[2] at presentation?
    - Yes → • BCT[2] with axillary surgery[3] **or** • Total mastectomy with axillary lymph node surgery with or without reconstruction[4]
    - No → • Total mastectomy with SLN[7] surgery with or without reconstruction[4] • Consider neoadjuvant endocrine therapy, if patient is interested in BCT (see Appendix C)
- For adverse features (large nodal burden, high *Ki-67*, high grade) → • Neoadjuvant chemotherapy (see Appendix B) followed by definitive surgery[8] and endocrine therapy (see Appendix C) • See Page 6 for evaluation during and upon completion of chemotherapy

TREATMENT

- Pathologically node negative → • Consider genomic testing for risk stratification to guide chemotherapy[5] (see Appendix A for genomic testing and indications for chemotherapy) • See Appendix B and Appendix C for treatment options, if indicated • See Page 7 for radiation therapy
- Pathologically node positive → Meets Z0011 criteria[6]?
  - 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

→ • Adjuvant chemotherapy (see Appendix B) followed by adjuvant endocrine therapy (see Appendix C) • See Page 7 for radiation therapy • Consider genomic testing (see Appendix A) if limited nodal disease and other favorable prognostic factors are present

BCT = breast conservation therapy
ER = estrogen receptor
HR = hormone receptor
PR = progesterone 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] 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] 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

[8] Definitive surgery should be considered if contraindications to systemic therapy

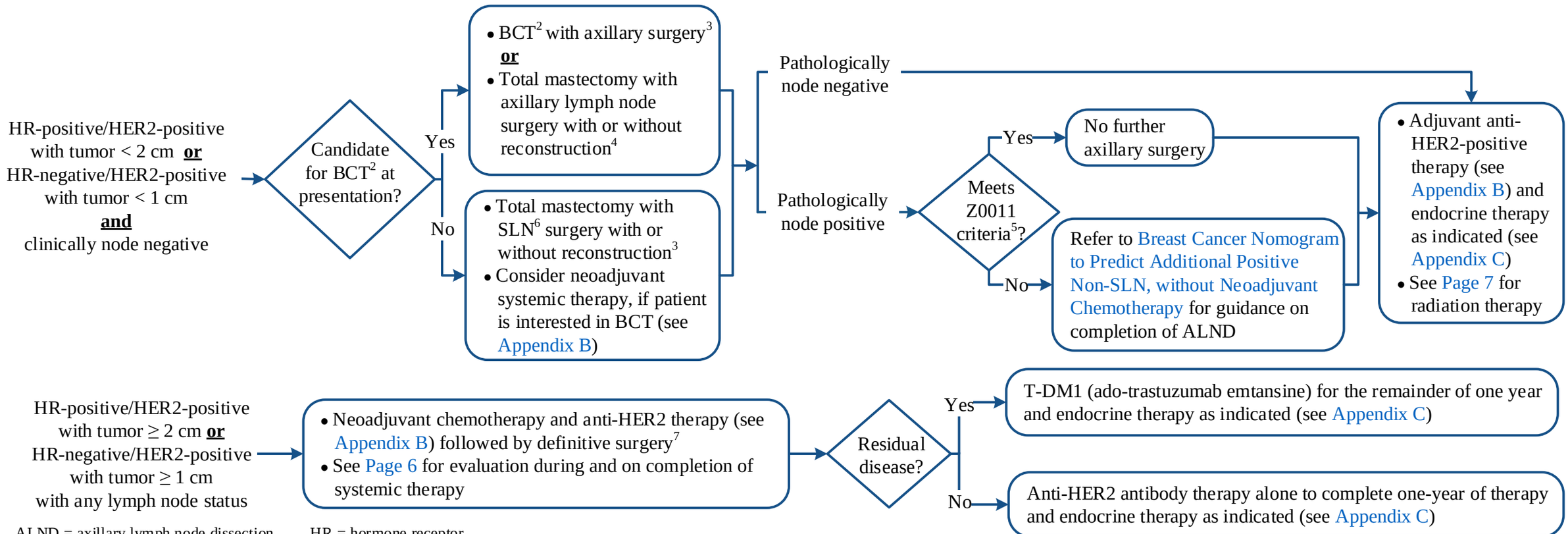
Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

Breast Cancer – Invasive Stage I-III

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

SURGICAL CONSIDERATIONS[1]

TREATMENT BASED ON PATHOLOGIC FINDINGS



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

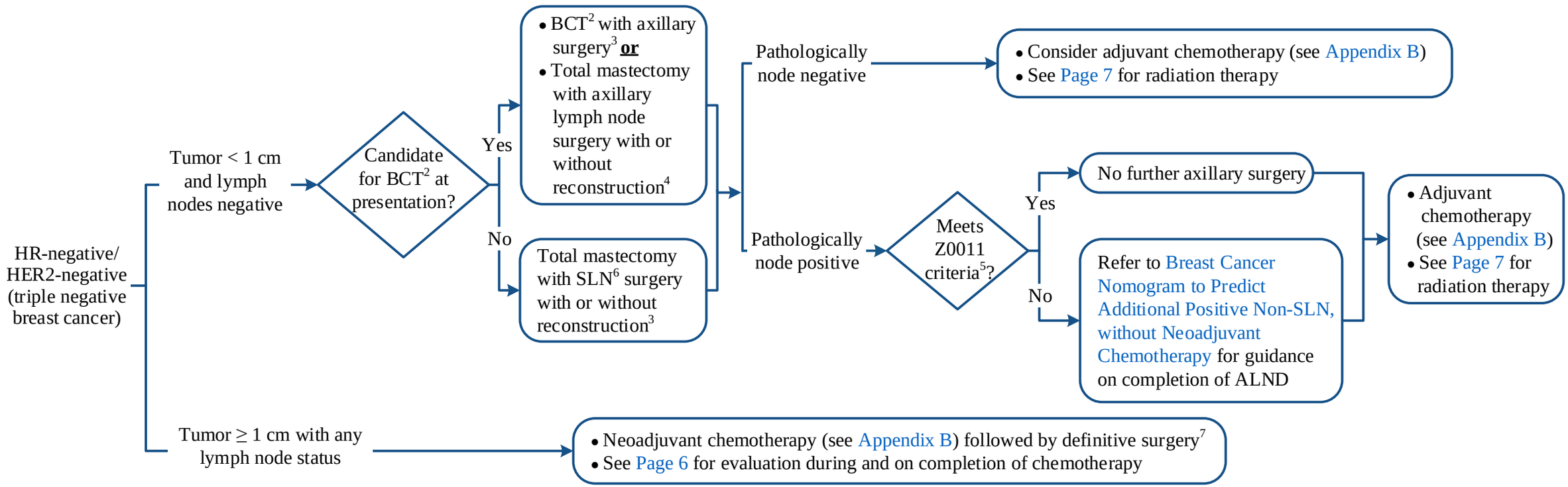
Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

Breast Cancer – Invasive Stage I-III

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

SURGICAL CONSIDERATIONS[1]

TREATMENT BASED ON PATHOLOGIC FINDINGS



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

Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

Breast Cancer – Invasive Stage I-III

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[1]
- 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

BCT candidate[2]?

SURGICAL OPTIONS

Yes

Breast conserving surgery[2]:

- If clinically node negative at diagnosis, proceed with sentinel node surgery[3] 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[4] 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

No

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

- If clinically node negative at diagnosis, proceed with sentinel node biopsy[3] 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[4] 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[5]

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

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

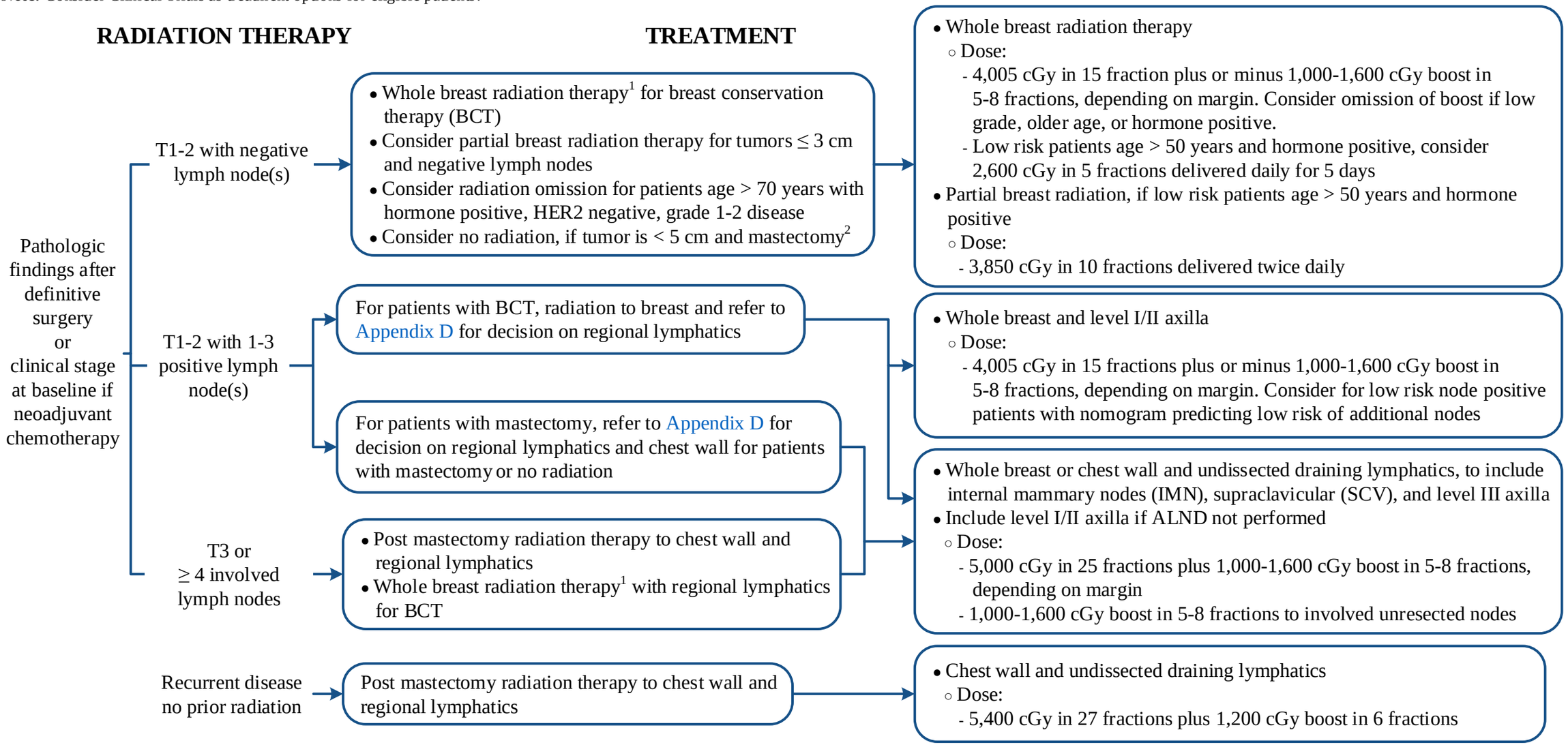
[4] Limited nodal involvement at presentation is defined as ≤ 3 abnormal nodes on axillary ultrasound. The largest biopsy proven positive node should be clipped at presentation and documentation of clipped nodes is required at surgery.

[5] For patients with stage II disease requiring post-mastectomy radiation, consider delayed reconstruction. For patients with stage III disease, delayed reconstruction is preferred.

Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

Breast Cancer – Invasive Stage I-III

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



[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

Breast Cancer – Invasive Stage I-III

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

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

Breast Cancer – Invasive Stage I-III

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

Distant metastasis?

- Yes → See NCCN guidelines
- No → Local only recurrence
- No → Regional only **or** local and regional recurrence

TREATMENT FOR RECURRENCE

Local only 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 mastectmy and no prior radiation therapy[2] → Surgical resection if possible plus radiation therapy[3]

Regional only or local and regional recurrence

- Axillary recurrence → Surgical resection if possible plus radiation therapy[2,3] 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

Department of Clinical Effectiveness V16
Approved by Executive Committee of the Medical Staff on 09/15/2020

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

Genomic Assay	Benefit from Chemotherapy[1]	No Benefit from Chemotherapy
Oncotype DX® recurrence score (RS) ○ Age ≤ 50	RS ≥ 16	RS < 16
○ Age > 50	RS > 25	RS ≤ 25
EndoPredict® risk score (RS)	RS > 3.3287 (high)	RS < 3.3287 (low)
Prosigna™ recurrence score (RS)	RS ≥ 41	RS < 41
Breast Cancer Index recurrence score (RS)	RS ≥ 5	RS < 5

[1] These 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.

Harris, L., Ismaila, N., McShane, L., Andre, F., Collyar, D., Gonzalez-Angulo, A., . . . Hayes, D. (2016). Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 34*(10), 1134–1150. doi:10.1200/JCO.2015.65.2289

APPENDIX B: Chemotherapy and Anti-HER2 Neoadjuvant/Adjuvant Systemic Therapy Options[1]

HER2-negative disease

Preferred regimens:

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

Other regimens[2]

- 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/m^2 IV and cyclophosphamide 600 mg/m^2 IV followed by paclitaxel 80 mg/m^2 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/m^2 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[2]:

- 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

First Line Therapy	Considerations
• Premenopausal[1] at diagnosis ○ OFS plus AI[2,3] for 5 years ○ Tamoxifen for 5-10 years • Postmenopausal at diagnosis ○ AI[2,3] for 5-7 years (maximum of 10 years) ○ Tamoxifen for 5-10 years only if AI[4] not possible	• Premenopausal ○ Consider OFS plus tamoxifen for patients who cannot tolerate AI • Postmenopausal ○ Consider adjuvant bisphosphonate for postmenopausal women

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 post menopausal (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

pN1 (macromets, > 2 mm):

- Age ≤ 40 years, upfront surgery
- 3+ LNs, upfront surgery
- ypN+
- cT3 N1
- ER negative, upfront surgery
- Age < 50 years with recurrence score > 18, if known
- SLNB only and > 33% risk of additional nSLNS
- Age > 40 years, p1-2LN+, ER positive and meets at least two of the following criteria:
  - Luminal B (*Ki-67* > 20% or HER2 positive)
  - Grade 3
  - Lymphovascular space invasion (LVSI)
  - High genomic score
  - Medial tumor location

pN0, pN0(i+) or micromets:

- Meets at least 3 of the following criteria:
  - T3
  - N1(mic)
  - Multiple mic nodes
  - Medial tumor location
  - Age ≤ 45 years
  - Grade 3
  - LVSI
  - ER negative
  - Luminal B (high *Ki-67* > 20% or HER2 positive)
  - SLN only, > 33% nomogram risk
  - High genomic score

APPENDIX E: Recurrent Systemic Therapy Treatment Options

Chemotherapy

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-hziy
- Mitomycin C

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)
- Gemcitabine and carboplatin
- Docetaxel and capecitabine
- Gemcitabine and paclitaxel
- Ixabepilone/capecitabine

HER2 Based Therapies

First-line regimens for HER2-positive disease[1]: (patients with trastuzumab naïve disease or those who recurred after 6 to 12 months after adjuvant trastuzumab)
- 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[1]:
- T-DM1 (ado-trastuzumab emtansine) for recurrence (6 to 12 months from adjuvant trastuzumab)
- Trastuzumab plus lapatinib without cytotoxic therapy
- Fam-trastuzumab deruxtecan-nxki
- Trastuzumab plus capecitabine
- Tucatinib plus trastuzumab plus capecitabine
- Lapatinib plus capecitabine
- Trastuzumab plus other agent
- Neratinib plus capecitabine

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

[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/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

Continued on next page

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

Continued on next page

PRINCIPLES OF BREAST ONCOLOGIC SURGERY - continued

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-positive breast cancer
- 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

Albain, K., Barlow, W., Ravdin, P., Farrar, W., Burton, G., Ketchel, S., . . . Osborne, C. (2009). Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: A phase 3, open-label, randomised controlled trial. *Lancet, 374*(9707), 2055-2063. https://doi.org/10.1016/S0140-6736(09)61523-3

Andre, F., Ciruelos, E., Rubovszky, G., Campone, M., Loible, S. Rugo, H., . . . Juric, D. (2019). Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *New England Journal of Medicine, 380*(20), 1929-1940. doi:10.1056/NEJMoa1813904

Baselga, J., Campone, M., Piccart, M., Burris III, H. A., Rugo, H. S., Sahmoud, T., . . . Hortobagyi, G. (2012). Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *New England Journal of Medicine, 366*(6), 520-529. https://doi.org/10.1056/NEJMoa1109653

Baselga, J., Cortés, J., Kim, S., Im, S., Hegg, R., Im, Y., . . . Swain, S. (2012). Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *New England Journal of Medicine, 366*(2), 109-119. https://doi.org/10.1056/NEJMoa1113216

Bear, H., Anderson, S., Smith, R., Geyer, C., Mamounas, E., Fisher, B., . . . Wolmark, N. (2006). Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National surgical adjuvant breast and bowel project protocol B-27. *Journal of Clinical Oncology, 24*(13), 2019-2027. https://doi.org/10.1200/JCO.2005.04.1665

Buchholz, T. (2009). Radiation therapy for early-stage breast cancer after breast-conserving surgery. *New England Journal of Medicine, 360*(1), 63-70. https://doi.org/10.1056/NEJMct0803525

Buchholz, T., Theriault, R., Niland, J., Hughes, M., Ottesen, R., Edge, S., . . . Weeks, J. (2006). The use of radiation as a component of breast conservation therapy in National Comprehensive Cancer Network Centers. *Journal of Clinical Oncology, 24*(3), 361-369. https://doi.org/10.1200/JCO.2005.02.3127

Burstein, H., Lacchetti, C., Anderson, H., Buchholz, T., Davidson, N., Gelmon, K., . . . Griggs, J. (2016). Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression. *Journal of Clinical Oncology, 34*(14), 1689-1701. https://doi.org/10.1200/JCO.2015.65.9573

Cardoso, F., van't Veer, L., Bogaerts, J., Slaets, L., Viale, G., Delaloge, S., . . . Piccart, M. (2016). 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *The New England Journal of Medicine, 375*(8), 717–729. doi:10.1056/NEJMoa1602253

Caudle, A., Gonzalez-Angulo, A., Hunt, K., Liu, P., Pusztai, L., Symmans, W., . . . Meric-Bernstam, F. (2010). Predictors of tumor progression during neoadjuvant chemotherapy in breast cancer. *Journal of Clinical Oncology, 28*(11), 1821-1828. https://doi.org/10.1200/JCO.2009.25.3286

Caudle, A., Hunt, K., Kuerer, H., Meric-Bernstam, F., Lucci, A., Bedrosian, I., . . . Mittendorf, E. (2011). Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: A practice-changing trial. *Annals of Surgical Oncology, 18*(9), 2407-2412. https://doi.org/10.1245/s10434-011-1593-7

Caudle, A. S., Yang, W. T., Krishnamurthy, S., Mittendorf, E. A., Black, D. M., Gilcrease, M. Z., . . . Kuerer, H. M. (2016). Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: Implementation of targeted axillary dissection. *Journal of Clinical Oncology, 34*(10), 1072-1078. https://doi.org/10.1200/JCO.2015.64.0094

Caudle, A. S., Yang, W. T., Mittendorf, E. A., Black, D. M., Hwang, R., Hobbs, B., . . . Kuerer, H. M. (2015). Selective surgical localization of axillary lymph nodes containing metastases in patients with breast cancer: A prospective feasibility trial. *JAMA Surgery, 150*(2), 137-143. doi:10.1001/jamasurg.2014.1086

Continued on next page

SUGGESTED READINGS - continued

Caudle, A. S., Yang, W. T., Mittendorf, E. A., Black, D. M., Hwang, R., Hobbs, B., . . . Kuerer, H. M. (2015). Selective surgical localization of axillary lymph nodes containing metastases in patients with breast cancer: A prospective feasibility trial. *JAMA Surgery, 150*(2), 137-143. doi:10.1001/jamasurg.2014.1086

Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, V., . . . Wang, Y. (2005). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet, 366*(9503), 2087-2106. doi:10.1016/s0140-6736(05)67887-7

Dickler, M., Tolaney, S., Rugo, H., Cortes, J., Dieras, V., Patt, D., . . . Baselga, J. (2017). MONARCH 1, A phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2(-) metastatic breast cancer. *Clinical Cancer Research, 23*(17), 5218-5224. doi:10.1158/1078-0432.CCR-17-0754

Esserman, L., Yau, C., Thompson, C., van 'T Veer, L., Borowsky, A., Hoadley, K., . . . Lindström, L. (2017). Use of molecular tools to identify patients with indolent breast cancers with ultralow risk over 2 decades. *JAMA Oncology, 3*(11), 1503–1510. doi:10.1001/jamaoncol.2017.1261

Fisher, B., Jeong, J., Anderson, S., Bryant, J., Fisher, E., & Wolmark, N. (2002). Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *The New England Journal of Medicine, 347*(8), 567-575. doi:10.1056/NEJMoa020128

Foulkes, W. D., Smith, I. E., & Reis-Filho, J. S. (2010). Triple-negative breast cancer. *The New England Journal of Medicine, 363*(20), 1938-1948. doi:10.1056/NEJMra1001389

Francis, P., Regan, M., Fleming, G., Lang, I., Ciruelos, E., Bellet, M., . . . Gelber, R. (2015). Adjuvant ovarian suppression in premenopausal breast cancer. *The New England Journal of Medicine, 372*(5), 436-446. doi:10.1056/NEJMoa1412379

Gianni, L., Eiermann, W., Semiglazov, V., Manikhas, A., Lluch, A., Tjulandin, S., . . . Baselga, J. (2010). Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet, 375*(9712), 377-384. doi:10.1016/S0140-6736(09)61964-4

Gianni, L., Pienkowski, T., Im, Y., Roman, L., Tseng, L., Liu, M., . . . Valagussa, P. (2012). Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. *The Lancet Oncology, 13*(1), 25-32. doi:10.1016/S1470-2045(11)70336-9

Giordano, S. H., Kuo, Y., Freeman, J. L., Buchholz, T. A., Hortobagyi, G. N., & Goodwin, J. S. (2005). Risk of cardiac death after adjuvant radiotherapy for breast cancer. *Journal of the National Cancer Institute, 97*(6), 419-424. doi:10.1093/jnci/dji067

Giuliano, A. E., Ballman, K., McCall, L., Beitsch, P. D., Brennan, M. B., Kelemen, P. R., . . . Morrow, M. (2017). Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA, 318*(10), 918–926. doi:10.1001/jama.2017.11470

Giuliano, A., Ballman, K., McCall, L., Beitsch, P., Whitworth, P., Blumencranz, P., . . . Hunt, K. (2016). Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: Long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Annals of Surgery, 264*(3), 413-420. doi:10.1097/SLA.0000000000001863

Harris, L., Ismaila, N., McShane, L., Andre, F., Collyar, D., Gonzalez-Angulo, A., . . . Hayes, D. (2016). Use of biomarkers to guide decisions on adjuvant systemic therapy forwomenwith early-stage invasive breast cancer: American Society of clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 34*(10), 1134–1150. doi:10.1200/JCO.2015.65.2289

Continued on next page

SUGGESTED READINGS - continued

Hortobagyi, G., Connolly, J., D'Orsi, C., Edge, S., Mittendorf, E., Rugo, H., . . . Giuliano, A. (2018). Breast. In M. B. Amin, S. Edge, F.Greene, D. R. Byrd, R. K. Brookland, M. K. Washington, J. E. Gershenwald, , C. C. Compton, K. R. Hess, D. C. Sullivan, J. M. Jessup, J. D. , Brierley, L. E. Gaspar, R. L. Schilsky, C. M. Balch, D. P. Winchester, E. A. Asare, M. Madera, D. M. Gress, & L. R. Meyer (Eds.), *AJCC cancer staging manual, eighth edition* (pp. 589-636). Chicago, IL: Springer.

Hunt, K., Euhus, D., Boughey, J., Chagpar, A., Feldman, S., Hansen, N., . . . Morrow, M. (2017). Society of Surgical Oncology Breast Disease Working Group statement on prophylactic (risk-reducing) mastectomy. *Annals of Surgical Oncology, 24*(2), 375–397. doi:10.1245/s10434-016-5688-z

Hunt, K., Yi, M., Mittendorf, E., Guerrero, C., Babiera, G., Bedrosian, I., . . . Meric-Bernstam, F. (2009). Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. *Annals of Surgery, 250*(4), 558-566. doi:10.1097/SLA.0b013e3181b8fd5e

Jones, S., Savin, M., Holmes, F., O'Shaughnessy, J., Blum, J., Vukelja, S., . . . Asmar, L. (2006). Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *Journal of Clinical Oncology, 24*(34), 5381-5387. doi:10.1200/JCO.2006.06.5391

Kelly, C., & Hortobagyi, G. (2010). Adjuvant chemotherapy in early-stage breast cancer: What, when, and for whom? *Surgical Oncology Clinics of North America, 19*(3), 649-668. doi:10.1016/j.soc.2010.03.007

Lucci, A., McCall, L., Beitsch, P., Whitworth, P., Reintgen, D., Blumencranz, P., . . . Giuliano, A. (2007). Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology group trial Z0011. *Journal of Clinical Oncology, 25*(24), 3657-3663. doi:10.1200/JCO.2006.07.4062.

Lynparza® [package insert] Retrieved from https://www.azpicentral.com/lynparza_tb/pi_lynparza_tb.pdf#page=1

Masuda, N., Lee, S., Ohtani, S., Im, Y., Lee, E., Yokota, I., . . . Toi, M. (2017). Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *New England Journal of Medicine, 376*(22), 2147-2159. doi:10.1056/NEJMoa1612645

McBride, A., Allen, P., Woodward, W., Kim, M., Kuerer, H., Drinka, E., . . . Buchholz, T. (2014). Locoregional recurrence risk for patients with T1,2 breast cancer with 1-3 positive lymph nodes treated with mastectomy and systemic treatment. *International Journal of Radiation Oncology, Biology, Physics, 89*(2), 392–398. https://doi.org/10.1016/j.ijrobp.2014.02.013

McGale, P., Taylor, C., Correa, C., Cutter, D., Duane, F., Ewertz, M., . . . Darby, S. (2014). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet, 383*(9935), 2127-2135. doi:10.1016/s0140-6736(14)60488-8

Mehta, R., Barlow, W., Albain, K., Vandenberg, T., Dakhil, S., Tirumali, N., . . . Hortobagyi, G. (2012). Combination anastrozole and fulvestrant in metastatic breast cancer. *New England Journal of Medicine, 367*(5), 435-444. doi:10.1056/NEJMoa1201622

von Minckwitz, G., Huang, C., Mano, M., Loibl, S., Mamounas, E., Untch, M., . . . Geyer, C. (2019). Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *New England Journal of Medicine, 380*(7), 617–628. doi:10.1056/NEJMoa1814017

Mittendorf, E., Boughey, J., Degnim, A., Harrell, R., Bassett, R., Yi, M., . . . Hwang, R. (2010). Size matters: Incorporation of sentinel lymph node (SLN) metastasis size into a nomogram predicting nonSLN involvement in SLN positive breast cancer patients. *Cancer Research, 70*(24). doi:10.1158/0008-5472.SABCS10-PD06-08

Mittendorf, E., Buchholz, T., Tucker, S., Meric-Bernstam, F., Kuerer, H., Gonzalez-Angulo, A., . . . Hunt, K. (2013). Impact of chemotherapy sequencing on local-regional failure risk in breast cancer patients undergoing breast-conserving therapy. *Annals of Surgery, 257*(2), 173-179. doi:10.1097/SLA.0b013e3182805c4a

Continued on next page

SUGGESTED READINGS - continued

National Comprehensive Cancer Network. (2020). *Breast Cancer* (NCCN Guideline Version 5.2020). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Paik, S., Tang, G., Shak, S., Kim, C., Baker, J., Kim, W., . . . Wolmark, N. (2006). Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor–positive breast cancer. *Journal of Clinical Oncology, 24*(23), 3726-3734. doi:10.1200/JCO.2005.04.7985

Piccart-Gebhart, M. J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., . . . Gelber, R. (2005). Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine, 353*(16), 1659-1672. doi:10.1056/NEJMoa052306

Pritchard, K. I., Shepherd, L. E., O'Malley, F. P., Andrulis, I. L., Tu, D., Bramwell, V. H., & Levine, M. N. (2006). HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *New England Journal of Medicine, 354*(20), 2103-2111. doi:10.1056/NEJMoa054504

Rosenkranz, K. M., Ballman, K., McCall, L., Kubicky, C., Cuttino, L., Le-Petross, H., Hunt, K. K., . . . Boughey, J. C. (2018). The feasibility of breast-conserving surgery for multiple ipsilateral breast cancer: An initial report from ACOSOG Z11102 (Alliance) trial. *Annals of Surgical Oncology, 25*(10), 2858–2866. https://doi.org/10.1245/s10434-018-6583-6

Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer, C. E., Davidson, N. E., . . . Wolmark, N. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine, 353*(16), 1673-1684. doi:10.1056/NEJMoa052122

Schneeweiss, A., Chia, S., Hickish, T., Harvey, V., Eniu, A., Hegg, R., . . . Cortés, J. (2013). Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). *Annals of Oncology, 24*(9), 2278-2284. doi:10.1093/annonc/mdt182

Sharma, R., Bedrosian, I., Lucci, A., Hwang, R., Rourke, 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/10.1245/s10434-010-1089-x

Sledge, G., Toi, M., Neven, P., Sohn, J., Inoue, K., Pivot, X., . . . Llombart-Cussac, A. (2017). MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *Journal of Clinical Oncology, 35*(25), 2875-2884. doi:10.1200/JCO.2017.73.7585

Smith, B., Arthur, D., Buchholz, T., Haffty, B., Hahn, C., Hardenbergh, P., . . . Harris, J. R. (2009). Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Journal of the American College of Surgeons, 209*(2), 269-277. doi:10.1016/j.jamcollsurg.2009.02.066

Smith, B. D., Haffty, B. G., Buchholz, T. A., Smith, G. L., Galusha, D. H., Bekelman, J. E., & Gross, C. P. (2006). Effectiveness of radiation therapy in older women with ductal carcinoma in situ. *Journal of the National Cancer Institute, 98*(18), 1302-1310. doi:10.1093/jnci/djj359

Smith, B. D., Haffty, B. G., Smith, G. L., Hurria, A., Buchholz, T. A., & Gross, C. P. (2008). Use of postmastectomy radiotherapy in older women. *International Journal of Radiation Oncology, Biology, Physics, 71*(1), 98-106. doi:10.1016/j.ijrobp.2007.09.006

Sparano, J., Gray, R., Makower, D., Pritchard, K., Albain, K., Hayes, D., . . . Sledge, G. (2015). Prospective validation of a 21-gene expression assay in breast cancer. *The New England Journal of Medicine, 373*(21), 2005–2014. doi:10.1056/NEJMoa1510764

Sparano, J., Gray, R., Makower, D., Pritchard, K., Albain, K., Hayes, D., . . . Sledge, G. (2018). Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *The New England Journal of Medicine, 379*(2), 111–121. doi:10.1056/NEJMoa1804710

Continued on next page

SUGGESTED READINGS - continued

Symmans, W. F., Peintinger, F., Hatzis, C., Rajan, R., Kuerer, H., Valero, V., . . . Pusztai, L. (2007). Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *Journal of Clinical Oncology, 25*(28), 4414-4422. doi:10.1200/JCO.2007.10.6823

Tolaney, S., Barry, W., Dang, C., Yardley, D., Moy, B., Marcom, P., . . . Winer, E. (2015). Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *New England Journal of Medicine, 372*(2), 134-141. doi:10.1056/NEJMoa1406281

Veronesi, U., Viale, G., Paganelli, G., Zurrida, S., Luini, A., Galimberti, V., . . . Vezzoli, D. (2010). Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. *Annals of Surgery, 251*(4), 595-600. doi:10.1097/SLA.0b013e3181c0e92a

Verzenio™ [package insert] Retrieved from http://pi.lilly.com/us/verzenio-us-ppi.pdf

Yamauchi, H., Woodward, W. A., Valero, V., Alvarez, R. H., Lucci, A., Buchholz, T. A., . . . Ueno, N. T. (2012). Inflammatory breast cancer: What we know and what we need to learn. *Oncologist, 17*(7), 891-899. doi:10.1634/theoncologist.2012-0039

Zejula® [package insert] Retrieved from https://nerlynx.com/pdf/full-prescribing-information.pdf

DEVELOPMENT CREDITS

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

Sausan Abouharb, MD (Breast Medical Oncology)
Beatriz Adrada, MD (Breast Imaging)
Catherine Akay, MD (Breast Surgical Oncology)
Constance Albarracin, MD, PhD (Pathology)
Elsa Arribas, MD (Breast Imaging)
Banu K. Arun, MD (Breast Medical Oncology)
Carlos Barcenas, MD (Breast Medical Oncology)
Robert C. Bast, MD (Translational Research)
Isabelle Bedrosian, MD (Breast Surgical Oncology)
Shon Black, MD (Breast Surgical Oncology)
Daniel J. Booser, MD (Breast Medical Oncology)
Abenaa Brewster, MD (Clinical Cancer Prevention)
Powel Brown, MD, PhD (Clinical Cancer Prevention)
Aman U. Buzdar, MD (Clinical Research)
Abigail Caudle, MD (Breast Surgical Oncology)
Mariana Chavez-Mac Gregor, MD (Health Services Research Clinical)
Cristina Checka, MD (Breast Surgical Oncology)
Hui Chen, MD (Anatomical Pathology)
Alejandro Contreras, MD (Anatomical Pathology)
Sarah DeSnyder, MD (Breast Surgical Oncology)
Mark Dryden, MD (Breast Imaging)
Mary Edgerton, MD, PhD (Anatomical Pathology)
Richard Ehlers, MD (Breast Surgical Oncology)
Barry Feig, MD (Surgical Oncology)
Elizabeth FitzSullivan, MD (Breast Surgical Oncology)
Wendy Garcia, BS♦
Sharon Giordano, MD (Health Services Research Clinical)
Tamara Haygood, MD, PhD (Diagnostic Radiology)
Karen Hoffman, MD (Radiation Oncology)
Gabriel N. Hortobagyi, MD (Breast Medical Oncology)Ŧ
Kelly K. Hunt, MD (Breast Surgical Oncology)Ŧ
Lei Huo, MD, PhD (Anatomical Pathology)
Rosa Hwang, MD (Breast Surgical Oncology)
Nuhad K. Ibrahim, MD (Breast Medical Oncology)
Meghan Karuturi, MD (Breast Medical Oncology)
Kimberly Koenig, MD (Breast Medical Oncology)

Ŧ Core Development Team
♦ Clinical Effectiveness Development Team

Continued on next page

DEVELOPMENT CREDITS - continued

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

Savitri Krishnamurthy, MD (Anatomical Pathology)
Henry M. Kuerer, MD, PhD (Breast Surgical Oncology)
Deanna Lane, MD (Diagnostic Radiology)
Huong Le-Petross, MD (Diagnostic Radiology)
Jennifer Litton, MD (Breast Medical Oncology)[Ŧ]
Anthony Lucci, MD (Breast Surgical Oncology)
Funda Meric-Bernstam, MD (Investigational Cancer Therapeutics)
Lavinia Middleton, MD (Anatomical Pathology)
Makesha Miggins, MD (Breast Surgical Oncology)
Melissa P. Mitchell, MD, PhD (Radiation Oncology)[Ŧ]
Tanya Moseley, MD (Diagnostic Radiology)
Stacy Moulder, MD (Breast Medical Oncology)
Rashmi Murthy, MD (Breast Medical Oncology)
George Perkins, MD (Radiation Oncology)
Matthew Piotrowski, MD (Breast Surgical Oncology)
Ana Refinetti, MD (Breast Surgical Oncology)
Erika Resetkova, MD, PhD (Anatomical Pathology)
Merrick I. Ross, MD (Surgical Oncology)
Aysegul A. Sahin, MD (Anatomical Pathology)
Lumarie Santiago, MD (Diagnostic Radiology)
Simona Shaitelman, MD (Radiation Oncology)
Puneet Singh, MD (Breast Surgical Oncology)
Benjamin Smith, MD (Radiation Oncology)
Nour Sneige, MD (Anatomical Pathology)
Michael Stauder, MD (Radiation Oncology)
Eric Strom, MD (Radiation Oncology)
Jessica Suarez Colen, MD (Breast Surgical Oncology)
Susie Sun, MD (Breast Surgical Oncology)
William Fraser Symmans, MD (Anatomical Pathology)
Mediget Teshome, MD (Breast Surgical Oncology)
Debu Tripathy, MD (Breast Medical Oncology)[Ŧ]
Naoto T. Ueno, MD, PhD (Breast Medical Oncology)
Vicente Valero, MD (Breast Medical Oncology)
Ronald Walters, MD (Medical Operations & Informatics)
Mary Lou Warren, DNP, APRN, CNS-CC[♦]
Gary Whitman, MD (Diagnostic Radiology)
Wendy Woodward, MD, PhD (Radiation Oncology)
Yun Wu, MD, PhD (Anatomical Pathology)
Wei Yang, MD (Diagnostic Radiology)

[Ŧ] Core Development Team
[♦] Clinical Effectiveness Development Team