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

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[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 (*e.g.*, 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]
- Bilateral diagnostic mammography **and**
- Ultrasound of breast(s) and regional nodal basins with FNA or core biopsy
- Based on imaging and/or clinical indications, MRI breast with and without contrast may be considered
- 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[5]) → Definitive breast and nodal surgery (see Page 3); If unfavorable breast to tumor size ratio and patient desires BCT[6], consider neoadjuvant endocrine therapy
- For adverse features (large nodal burden, high *Ki*-67[7], high grade) → Consider neoadjuvant chemotherapy (see Page 4)

HR-positive/ HER2-positive[8]

- 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 **or** tumor of any size with nodal involvement → Neoadjuvant systemic therapy (see Page 5)

HR-negative/ HER2-positive[8]

- 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 anti-HER2 and chemotherapy (see Page 5)

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

- Tumor < 1 cm and lymph nodes negative → Definitive surgery and sentinel lymph node biopsy (see Page 6)
- Tumor ≥ 1 cm with any lymph node status → Neoadjuvant systemic therapy (see Page 6)

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 clinical stage IIB or higher, or signs or symptoms suggestive of metastatic disease should be considered for additional imaging
[5] Low *Ki-67* is defined as below institutional median value
[6] High *Ki-67* is defined as above institutional median value
[7] Candidates for BCT: • Tumor to breast size ratio allows for acceptable cosmetic result • No evidence of diffuse calcifications on mammogram
[8] HER2-positive by either immunohistochemistry 3+ or FISH, (HER2/CEP17 ratio ≥ 2 or HER2 copy number ≥ 6)

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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*[2]) **and** cN0 → Candidate for BCT[3] at presentation?
  - Yes → BCT **or** total mastectomy with sentinel lymph node biopsy (SLNB) with or without reconstruction[4]
  - No → Total mastectomy with SLNB with or without reconstruction[4]
- Favorable characteristics (grade I/II, strongly ER/PR positive, low *Ki-67*[2]) **and** cN1(1-3 abnormal level 1/II nodes on ultrasound)[7,8,9] → Candidate for BCT[3] at presentation?
  - Yes → BCT
  - No → Total mastectomy with or without reconstruction[4]
- For adverse features (large nodal burden, high *Ki-67*, high grade) → See Page 4

TREATMENT

- pN0
  - Consider gene expression testing for risk stratification to guide chemotherapy[5] (see Appendix A for gene expression testing and indications for chemotherapy)
  - See Appendix B and Appendix C for treatment options, if indicated
  - See Page 8 for radiation therapy
- pN1 → Meets ACOSOG Z0011 **or** AMAROS **or** IBCSG 2301 criteria[6]?
  - Yes → No further axillary surgery
  - No → Level I/II axillary dissection
  - → Level I/II axillary dissection[10, 11]

Then:
- Adjuvant chemotherapy (see Appendix B) followed by adjuvant endocrine therapy (see Appendix C)
- See Page 8 for radiation therapy
- Consider gene expression testing (see Appendix A) if limited nodal disease and other favorable prognostic factors are present

ACOSOG = American College of Surgeon Oncology Group
AMAROS = After Mapping of the Axilla: Radiotherapy Or Surgery
BCT = breast conservation therapy
ER = estrogen receptor
HR = hormone receptor
IBCSG = International Breast Cancer Study Group
PR = progesterone receptor
SLND = sentinel lymph node dissection

[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] Low *Ki-67* is defined as below institutional median value
[3] Candidates for BCT: • Tumor to breast size ratio allows for acceptable cosmetic result • No evidence of diffuse calcifications on mammogram
[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] Gene expression testing may not be indicated for post-surgery patients with all favorable prognostic factors present
[6] See Appendix D
[7] A positive lymph node identified on preoperative ultrasound should be clipped at the time of biopsy and every effort should be made to remove the clipped node at the time of surgery
[8] Retrospective institutional data suggest that patients with ultrasound detected metastases, even if small volume, have a higher burden of nodal involvement than patients with SLND-detected metastases
[9] Chemotherapy is not indicated in postmenopausal patients with 1-3 positive nodes and a gene expression recurrence score of ≤ 25. For premenopausal patients, chemotherapy is recommended in node positive patients regardless of the recurrence score. The plan for surgical management of the axilla in the context of menopausal status and timing of systemic therapy should be discussed with the medical oncologist.
[10] Level I/II dissection is the current standard of care for patients with cN1 disease undergoing up front surgery.
[11] As delineated in recommendations by the National Comprehensive Cancer Network (NCCN), up front targeted axillary dissection can be considered in selected patients with multidisciplinary input. Please note these data are not supported by level 1 evidence and this approach is an active area of investigation within our institution.

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

SURGICAL CONSIDERATIONS[1]

TREATMENT

HR-positive/ HER2-negative → For adverse features (large nodal burden[2], high *Ki-67*[3], high grade) →

- Neoadjuvant chemotherapy[4] (see Appendix B) followed by definitive surgery[5] and endocrine therapy (see Appendix C)
- See Page 7 for evaluation during chemotherapy and definitive surgery recommendations

BCT = breast conservation therapy
HR = hormone receptor

[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] Large nodal burden is defined as clinical node positive disease with ≥ 4 level I/II suspicious lymph nodes on ultrasound
[3] High *Ki-67* is defined as above institutional median value
[4] Consider neoadjuvant systemic therapy for patients with large tumors interested in BCT
[5] Definitive surgery should be considered if contraindications to systemic therapy

Breast Cancer – Invasive Stage I-III

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

SURGICAL CONSIDERATIONS[1]

TREATMENT BASED ON PATHOLOGIC FINDINGS

HR-positive/HER2-positive with tumor < 1 cm **or** HR-negative/HER2-positive with tumor < 1 cm **and** cN0

→ Candidate for BCT[2] at presentation?

- Yes → BCT **or** total mastectomy with sentinel lymph node biopsy (SLNB) with or without reconstruction[3]
- No → Total mastectomy with SLNB with or without reconstruction[3]

→ pN0 → • Adjuvant anti-HER2-positive therapy (see Appendix B) and endocrine therapy as indicated (see Appendix C)
• See Page 8 for radiation therapy

→ pN1 → Meets ACOSOG Z0011 **or** AMAROS **or** IBCSG 2301 criteria[4]?

- Yes → No further axillary surgery → • Adjuvant anti-HER2-positive therapy (see Appendix B) and endocrine therapy as indicated (see Appendix C)
  • See Page 8 for radiation therapy
- No → Level I/II axillary dissection → • Adjuvant anti-HER2-positive therapy (see Appendix B) and endocrine therapy as indicated (see Appendix C)
  • See Page 8 for radiation therapy

HR-positive/HER2-positive with tumor ≥ 1 cm **or** tumor of any size with nodal involvement **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[5]
• See Page 7 for evaluation during systemic therapy and definitive surgery recommendations

→ Residual disease?

- Yes → T-DM1 (ado-trastuzumab emtansine) for 14 total doses 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)

ACOSOG = American College of Surgeon Oncology Group
ALND = axillary lymph node dissection
AMAROS = After Mapping of the Axilla: Radiotherapy Or Surgery
BCT = breast conservation therapy
HR = hormone receptor

[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] 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.
[4] See Appendix D
[5] Definitive surgery should be considered if contraindications to systemic therapy

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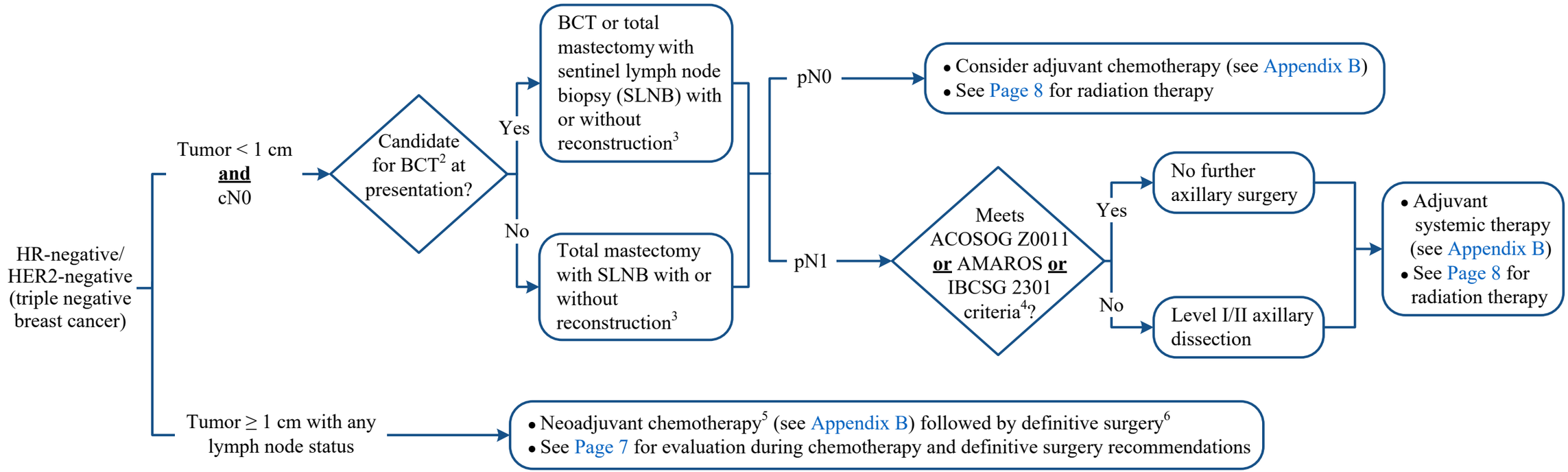
Note: Consider Clinical Trials as treatment options for eligible patients.

SURGICAL CONSIDERATIONS[1]

TREATMENT BASED ON PATHOLOGIC FINDINGS



ACOSOG = American College of Surgeon Oncology Group
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[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] 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.
[4] See Appendix D
[5] Add pembrolizumab for cT1cN1 or T2N0 or greater
[6] Definitive surgery should be considered if contraindications to systemic therapy

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
- At completion of systemic treatment[1]:
  - Ipsilateral diagnostic mammography **and**
  - Ultrasound of breast(s) and/or MRI breast with and without contrast
  - If clinically indicated, ultrasound of nodal basin(s)
- At any point for clinical suspicion of disease progression, consider mid-treatment MRI breast with and without contrast[2] (preferred) **or** ultrasound of breast and nodal basin(s)
  - If clinical progression, consider change in systemic therapy or proceed with surgery if resectable

BCT candidate[2]?

SURGICAL OPTIONS

Yes

Breast conserving surgery[3]:
- If clinically node negative at diagnosis, proceed with sentinel node biopsy followed by axillary lymph node dissection if sentinel node is positive
- If clinically node positive, confirmed by needle biopsy proceed with axillary lymph node dissection or if axillary nodal disease limited at presentation[4] and is no longer evident, consider SLNB with documented removal of clipped node and if no residual disease 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 followed by axillary lymph node dissection if sentinel node positive
- If clinically node positive, confirmed by needle biopsy proceed with axillary lymph node dissection or if limited axillary nodal disease at presentation[4] and no longer evident on imaging consider SLNB 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 8 for radiation therapy

BCT = breast conservation therapy
SLNB = sentinel lymph node biopsy

[1] Imaging may be helpful for assessing response as predictive/prognostic information, even if surgical management is not impacted in the setting of mastectomy
[2] Neoadjuvant response assessment with MRI in cases where mammography and/or ultrasound are insufficient
[3] 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

[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.

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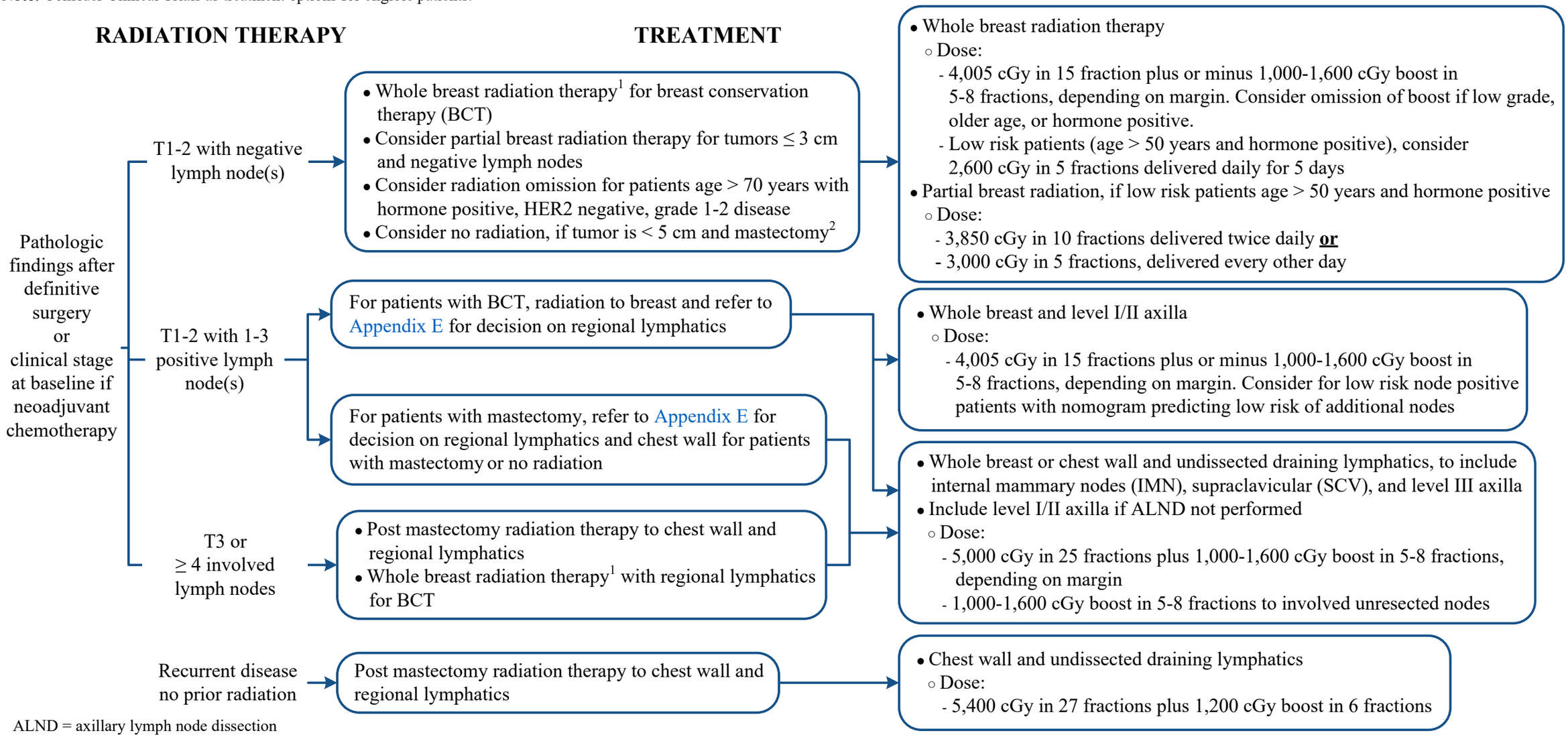
Breast Cancer – Invasive Stage I-III

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



ALND = axillary lymph node dissection

[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 gene expression scores, or patients eligible for partial breast irradiation, radiation therapy may be delivered before chemotherapy.

[2] See Appendix E: 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
- Imaging recommendations:
  - Routine imaging of the chest wall or reconstructed breast following mastectomy is not indicated
  - Diagnostic mammography[1,2] with or without tomosynthesis at 6 months following completion of radiation therapy for patients with breast conservation therapy, then annually for the first 5 years, followed by annual screening mammography thereafter (see Survivorship - Invasive Breast Cancer algorithm)
- Postmenopausal patients receiving tamoxifen should have close monitoring for symptoms of uterine cancer or endometrial hyperplasia
- Assess bone health (see Survivorship - Breast Cancer: Bone Health algorithm)
- Encourage age appropriate cancer and general health guidelines
- Prospective lymphedema screening program
- Lymphedema management as needed. If a compression sleeve is prescribed, then change at least every 6 months.
- Referral to Physical Therapy for improving range of motion
- Consider referral to Physical Medicine and Rehabilitation for radiation induced restricted range of motion unrelieved by physical therapy, with consideration for minimally invasive procedures and pharmacologic interventions
- Consider referral to Plastic Surgery for discussion of surgical interventions to reduce radiation fibrosis or symptoms of lymphedema

→ See Page 10 for Evaluation for Local Recurrence

[1] Diagnostic mammography for up to 5 years post diagnosis then screening mammography thereafter

[2] Consider additional MRI breast with and without contrast annually for patients with germline mutations (see Appendix A in the Breast Cancer Screening algorithm for type of mutation and recommended screening interval) **or** diagnosis prior to age 50 years and have dense breasts[3]. Alternating mammography and MRI breast every 6 months is suggested if feasible.
Note: Additional imaging can be considered as delineated in the recommendation from the American College of Radiology (ACR) and the American Cancer Society (ACS). Note that the data supporting these guidelines are outdated (as per our internal analysis) and additional imaging is not recommended by the National Comprehensive Cancer Network (NCCN) survivorship guidelines.

[3] Dense breast is defined as heterogeneously dense or extremely dense

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)
- Diagnostic mammography (bilateral, if intact breast)

and

- MRI breast with and without contrast
- If clinically indicated, ultrasound of regional nodal basins
- Body imaging for invasive recurrence
- Multidisciplinary team discussion to determine appropriate sequencing of treatment options

→ Distant metastasis?

Yes
- See Breast Cancer – Metastatic Disease algorithm
- Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with with Patient Representative[2]

No

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[3]
- For resectable cases, consider preoperative systemic therapy, as per tumor subtype

Initial treatment with mastectomy plus level I/II axillary dissection and prior radiation therapy →
- Surgical resection if possible[3,4]
- For resectable cases, consider preoperative systemic therapy, as per tumor subtype

Initial treatment with mastectomy and no prior radiation therapy[3] →
- Surgical resection[4] if possible plus radiation therapy[4,5]
- For resectable cases, consider preoperative systemic therapy, as per tumor subtype

Regional only or local and regional recurrence

Axillary recurrence →
- Surgical resection if possible plus radiation therapy[3,4,5] if possible
- For resectable cases, consider preoperative systemic therapy, as per tumor subtype

Supraclavicular recurrence →
- Radiation therapy[3,4,5] if possible
- Consider systemic therapy, as per tumor subtype, prior to radiation therapy

Internal mammary node recurrence →
- Radiation therapy[3,5] if possible
- Consider systemic therapy, as per tumor subtype, prior to radiation therapy

→
- Adjuvant systemic therapy may be helpful in HR-negative case (see Appendix B)
- Adjuvant endocrine therapy with an agent not previously given as applicable may be helpful in HR-positive cases (see Appendix C)
- For unresectable cases, use of options used for metastatic therapy (refer to Breast Cancer - Metastatic Disease algorithm) should be considered with re-evaluation for local therapy if response is seen

[1] Consider MD Anderson approved breast biomarkers
[2] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
[3] Consider referral to radiation therapy for evaluation of re-irradiation if prior treatment > 2 years and for potential clinical benefit
[4] If local treatment with surgery and/or radiation is not possible, re-evaluate if response to systemic therapy
[5] See Page 8 for radiation therapy

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APPENDIX A: Gene Expression Considerations for Determination of Prognosis and Need for Adjuvant Chemotherapy in Patients with Hormone receptor-positive/HER2-negative Breast Cancer

Gene expression assays supported by level 1 or 2 evidence:

Note: Except for Oncotype DX®, other assays and benefit risk score parameters are specific for node-negative cases

- 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

Gene Expression Assay	Benefit from Chemotherapy	No Benefit from Chemotherapy
Oncotype DX® recurrence score (RS) if node negative • Age ≤ 50	RS ≥ 16	RS < 16
• Age > 50	RS > 25	RS ≤ 25
Oncotype DX® recurrence score (RS) if 1-3 positive nodes • Post-menopausal women	RS > 25	RS ≤ 25
• Pre-menopausal women	Regardless of RS	N/A
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[1]	RS < 5

[1] Patients with Breast Cancer Index RS ≥ 5 derive significant benefit from extended endocrine therapy

Harris, L. N., Ismaila, N., McShane, L. M., Andre, F., Collyar, D. E., Gonzalez-Angulo, A. M., . . . Hayes, D. F. (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. https://doi.org/10.1200/JCO.2015.65.2289

Kalinsky, K., Barlow, W. E., Gralow, J. R., Meric-Bernstam, F., Albain, K. S., Hayes, D. F., . . . Hortobagyi, G. N. (2021). 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *The New England Journal of Medicine, 385*(25), 2336-2347. https://doi.org/10.1056/NEJMoa2108873

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

Sparano, J. A., Gray, R. J., Ravdin, P. M., Makower, D. F., Pritchard, K. I., Albain, K. S., . . . Sledge Jr., G. W. (2019). Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. *The New England Journal of Medicine, 380*(25), 2395-2405. https://doi.org/10.1056/NEJMoa1904819

APPENDIX B: Chemotherapy and Targeted Therapy Options for Neoadjuvant/Adjuvant Systemic Therapy[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[2]) for 4 cycles followed or preceded by weekly paclitaxel 80 mg/m^2 IV for 12 doses, or dose-dense paclitaxel 175 mg/m^2 IV every 2 weeks[2] for 4 cycles)
- 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 for 4 cycles followed or preceded by weekly paclitaxel 80 mg/m^2 IV for 12 doses)
- 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 for 4 cycles[2]

Other regimens[3]

- Dose-dense AC (doxorubicin and cyclophosphamide) for 4 cycles followed or preceded by docetaxel every 3 weeks for 4 cycles[2]
- Docetaxel and carboplatin (not routinely used except when there is no response to therapy or patient is borderline operable)[2]

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-THP (doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV followed by docetaxel 75 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 every 3 weeks for 4 cycles); AC (doxorubicin and cyclophosphamide) IV either every 3 weeks or every 2 weeks (dose-dense[2]) for 4 cycles. Paclitaxel (80 mg/m^2 IV weekly for 12 doses or 175 mg/m^2 every 3 weeks for 4 cycles) can be used in place of docetaxel.
- TCHP (docetaxel 75 mg/m^2 IV, carboplatin AUC 6 IV, trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg IV, pertuzumab 840 mg IV followed by 420 mg IV)[2,4] for 6 cycles
- Weekly paclitaxel 80 mg/m^2 IV plus trastuzumab 4 mg/kg IV loading dose, followed by 2 mg/kg IV (for low-risk disease, such as stage I) for 12 doses
- For stage II or higher, consider addition of pertuzumab with chemotherapy portion of regimen or for the entire year with the trastuzumab

Other regimens[3]:

- T-DM1 3.6 mg/kg IV for 14 cycles as adjuvant therapy after preoperative trastuzumab for residual HER2-positive disease
- Consider use of neratinib after completion of (neo)adjuvant chemotherapy/HER2 antibody therapy for patients with high risk tumors (*e.g.,* multiple positive nodes, locally advanced disease, etc.), particularly for hormone receptor-positive disease

T-DM1 = ado-trastuzumab emtansine

[1] Refer to National Comprehensive Cancer Network (NCCN) Guidelines for specific doses and number of cycles
[2] Granuloctye colony-stimulating factors (*e.g.,* filgrastim or pegfilgrastim) are recommended for use with this regimen
[3] May consider other neoadjuvant/adjuvant regimens per NCCN guidelines
[4] Consider omitting carboplatin with significant toxicities

Continued on next page

APPENDIX B: Chemotherapy and Targeted Therapy Options for Neoadjuvant/Adjuvant Systemic Therapy[1] - continued

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

Neoadjuvant regimen: Weekly paclitaxel 80 mg/m^2 IV for 12 doses with pembrolizumab 200 mg IV every 3 weeks **and** carboplatin AUC 1.5 IV weekly or carboplatin AUC 5 IV every 3 weeks for 12 weeks followed by AC[2] (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) IV with pembrolizumab 200 mg IV for 4 doses, then pembrolizumab 200 mg IV every 3 weeks or pembrolizumab 400 mg IV every 6 weeks to complete one year

Adjuvant regimen: Capecitabine for high-risk triple negative breast cancer with residual disease after neoadjuvant chemotherapy

Pathogenic germline BRCA 1 or 2 mutations: Olaparib 300 mg PO twice daily for 1 year following all local therapy (including radiation)

Adjuvant therapy indications:

- Following all local therapy (including radiation)
- HER2-negative only
- High risk cases (*e.g.,* TNBC, any node positive or tumor ≥ 2 cm, HR-positive/HER2-negative with ≥ 4 positive nodes)

Neoadjuvant therapy indications:

- TNBC with any residual invasive disease after neoadjuvant chemotherapy
- HR-positive with any residual invasive disease after neoadjuvant chemotherapy and CPS + EG score of 3

CPS = clinical and pathologic stage
EG = estrogen receptor status and histologic grade
TNBC = triple negative breast cancer

[1] Refer to National Comprehensive Cancer Network (NCCN) Guidelines for specific doses and number of cycles

[2] Granuloctye colony-stimulating factors (*e.g.*, filgrastim or pegfilgrastim) are recommended for use with this regimen

APPENDIX C: Endocrine Neoadjuvant/Adjuvant Therapy Options

Treatment	Considerations
• Stage I or II ○ Premenopausal[1] at diagnosis - OFS plus AI[2,3] for 5 years **or** - OFS with tamoxifen for 5 years **or** - Tamoxifen alone 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[3] not possible • Stage III ○ Premenopausal[1] at diagnosis - OFS plus AI[2,3] for at least 5 years **or** - OFS with tamoxifen for 5 years **or** - Tamoxifen alone for 5-10 years **and** - Abemaciclib for 2 years - Olaparib for BRCA 1/2 mutations followed by abemaciclib ○ Postmenopausal at diagnosis - AI[2,3] for at least 5 years **and** - Abemaciclib for 2 years - Olaparib for BRCA 1/2 mutations followed by abemaciclib	• Premenopausal ○ Consider OFS plus tamoxifen for patients who cannot tolerate AI • Postmenopausal ○ Consider adjuvant bisphosphonate for postmenopausal women

AI = aromatase inhibitor
OFS = ovarian function suppression

Note: 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 (BSO)], 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 and removal of ovaries are uncertain or < 55 years old, consider verifying with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels. If definitive BSO, verification with hormone levels is not indicated.
[3] Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy

APPENDIX D: Criteria for Omitting Axillary Node Dissection

Trial	Criteria
Z0011	cT1–T2, cN0, M0, no preoperative chemotherapy, lumpectomy and sentinel lymph node biopsy (SLNB), and tumor positive sentinel lymph node (SLN) with up to two nodes positive on SLNB, and are planned for whole breast irradiation and systemic therapy
AMAROS	cT1–T2, cN0, no preoperative chemotherapy, 1–2 positive SLNs. Adjuvant radiation therapy planned with intentional inclusion of undissected axilla at risk. Limited data exist for axillary management of mastectomy patients with positive lymph nodes, and multidisciplinary discussion is recommended.
IBCSG 2301	cT1–T2, cN0, no preoperative chemotherapy, 1–2 positive SLNs for micrometastasis (< 2 mm). 9% of patients in this trial underwent mastectomy and multidisciplinary discussion is recommended.

AMAROS = After Mapping of the Axilla: Radiotherapy Or Surgery
IBCSG = International Breast Cancer Study Group

APPENDIX E: 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 gene expression 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 gene expression score

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 mammography **and** ultrasound of breast(s) and regional nodal basins with fine needle aspiration (FNA) or core biopsy
- Based on imaging and/or clinical indications, MRI breast with and without may be considered
- 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 the inability to obtain a core 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 following needle biopsy of suspicious breast lesions
- Medical photography should be utilized in patients who present with skin changes
- Punch biopsy of the skin should be considered to document skin involvement

Operative Standards for Breast Oncologic Surgery

- Technical aspects and critical elements of breast cancer surgery impacting patient oncologic outcomes have been defined as per the Operative Standards for Cancer Surgery Vol 1. and should be met in each of the following operations when performed for breast cancer - breast conserving surgery, mastectomy, sentinel lymphadenectomy and axillary lymphadenectomy

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/multicentric malignancy when deemed appropriate by the multidisciplinary team. Resection of all gross disease with microscopically negative margins without violating the tumor itself during the course of the dissection.
- 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 or with 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. Specimen orientation should be achieved either by staining or painting the specimen or by marking the specimen with sutures to facilitate margin assessment by the pathologist.
- Intraoperative specimen radiography 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 mammography 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

- Incisions for total mastectomy should be placed to facilitate the removal of the preponderance of breast tissue to achieved local disease control and decrease the risk of recurrent breast cancer
- Anatomical boundaries of mastectomy remain uniform in order to remove the entire breast parenchyma. This includes the second rib superiorly, the upper border of the rectus sheath inferiorly, the lateral border of the sternum medially and the latissimus dorsi muscle laterally. Care should be taken to excise glandular tissue which extends into the axilla. Pectoralis fascia is commonly excised. Fascia of the serratus anterior and rectus sheath should be preserved.
- Mastectomy flaps should be elevated in a manner that facilitates the removal of essentially all breast tissue to reduce risk of recurrence and that preserves the overlying subcutaneous tissue and its vascular plexus to minimize the risk of flap necrosis.
- Localized excision of the pectoralis muscle is sometimes necessary to achieve clear margins.
- Drains must be optimally placed to prevent seroma formation and reduce seroma-related morbidity after total mastectomy in order to avoid delays to adjuvant treatment.
- 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 the 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 a 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 carriers, 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 the 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.
- Sentinel lymph node dissection:
  - 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%
  - All sentinel nodes must be identified, removed and subjected to pathologic analysis to ensure that sentinel node mapping and sentinel node lymphadenectomy provide accurate information for breast cancer staging. Sentinel nodes are defined by the presence of a tracer that has been previously injected into the affected breast or by the presence of a dominant palpable lymph node identified by the operating surgeon.
  - The site of localizing tracer or dye injection within the affected breast and/or subareolar plexus does not influence the identification of the axillary sentinel node(s)
  - For sentinel node identification using a radioactive tracer, pre-incision skin localization of the area or highest radioactivity facilitates a minimally invasive approach to exposure in the axilla and the identification of any extraaxillary sites of nodal drainage. Lymphoscintigraphy is not required for sentinel node localization unless extraaxillary site of drainage is suspected.

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PRINCIPLES OF BREAST ONCOLOGIC SURGERY - continued

Surgical staging of the axilla (continued)

- Targeted Axillary Dissection (TAD):
  - 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 following image-guided localization.
  - 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)
  - After neoadjuvant chemotherapy, dual tracer technique utilizing blue dye and technetium radioisotope is recommended to improve sentinel lymph node identification and to reduce the chance of a false negative sentinel node

Management of biopsy proven axillary disease

- Axillary lymph node dissection entails identification of the axillary vein and latissimus dorsi, pectoralis major, pectoralis minor, serratus anterior and subscapularis muscles is essential for the resection of sufficient level I and II axillary nodes for breast cancer staging and adjuvant treatment planning
- 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. Removal of level III nodes is not typically indicated but should be considered in patients with locally advanced breast cancer, N2 disease and if identified by palpation intraoperatively. Radiation therapy can be considered as an alternative in selected patients.
- Removal of Rotter's nodes is not typically indicated but should be considered in patients with locally advanced breast cancer, N2 disease and if identified as suspicious by preoperative imaging
- A target minimum of 10 axillary nodes should be removed to ensure a high-level confidence that the remaining lymph nodes are negative
- 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 a preoperative multidisciplinary discussion is required.
  - Patients with cT1-2, N0 tumors undergoing up front surgery with 1-2 positive SLNs, and will undergo lumpectomy or mastectomy along with adjuvant radiation therapy with intentional inclusion of undissected axilla at risk
  - Patients with cT1-2, N0 tumors undergoing up front surgery with nodal disease limited to micrometastasis defined as > 0. 2 mm and < 2 mm
- 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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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, 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 mammography (if recurrence after breast conserving surgery), 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 the recurrence is resectable at diagnosis, the patient 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.

Management of patients at high-risk for breast malignancy

- Patients with hereditary breast and ovarian cancer syndrome, deleterious BRCA1 and 2 mutations, a 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 mammograms 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, or with symptomatic fungating and/or bleeding tumors not responsive to systemic therapy

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