Breast Cancer – Inflammatory (IBC)

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

PRESENTATION

- Rapid onset ≤ 6 months of breast erythema and/or peau d'orange edema, and/or swollen breast, with or without an underlying palpable mass
- With or without nipple inversion
- Skin changes occupying at least one-third of the breast
- Breast swelling is often present
- Erythema may or may not be present

and

- Pathologic confirmation of breast cancer[1]

INITIAL EVALUATION

- History and physical
- Obtain bilateral breast photographs to establish baseline clinical appearance and follow up with medical photography for treatment response documentation
- Bilateral diagnostic mammography **and/or** tomosynthesis[2]
- MRI breast with and without contrast[3]
- Bilateral ultrasound of breast[4] and nodal basins[5] (include bilateral supraclavicular regions and contralateral nodes even if negative contralateral breast)
- Obtain ultrasound-guided core biopsy of tumor (MRI-guided biopsies if mass not present)
  - Consider skin punch biopsy in addition to breast parenchymal biopsy
- The IBC Scoring System[6] may be calculated to assist in diagnosing borderline cases
- Multidisciplinary evaluation

- CBC with differential, complete metabolic panel
- PET/CT scan - If PET/CT not possible, then CT chest/abdomen/pelvis with contrast and bone scan is acceptable. If cN3 disease is suspected (supraclavicular, infraclavicular), add CT neck to CT chest/abdomen/pelvis with contrast and bone scan.
- FNA or core biopsy[7] of an index suspicious nodes, if not already performed
- Clip placement of positive axillary node if required by surgery
- MRI brain if extracranial stage IV disease confirmed by PET/CT scan **or** if neurological symptoms (*e.g.*, headache, visual changes, etc.)
- Pathology review[8]:
  - HER2 (human epidermal growth factor receptor) status
  - ER, PR status
  - Composite histologic grade
  - Histologic type
  - Lymphatic/vascular invasion
- Germline BRCA testing for HER2 negative status

- Consider Plastic Surgery consult[9,10]
- Enroll in prospective lymphedema screening program
- Pre-operative lymphedema education
- Lifestyle risk assessment[11]
- IBC education
- Enroll in IBC registry[12]
- Consider need for genetic counseling, fertility preservation, and pregnancy testing
- Consider referral to body image therapist

See Page 2 for treatment based on staging

FNA = fine needle aspiration
ER = estrogen receptor
PR = progesterone receptor
pCR = pathological complete response

[1] If no confirmed epithelial cancer diagnosis, see Appendix A for evaluation of undiagnosed cancer
[2] For tertiary centers, mammogram of ipsilateral breast is not needed if outside mammogram of diagnostic quality was within 2 months and is available for review. IBC is painful and mammogram may not be tolerable for some patients.
[3] If suspicious MRI finding in the contralateral breast, then MRI-directed or second look ultrasound can be performed
[4] If MRI is performed, bilateral ultrasound of breast is not needed
[5] If PET/CT has been performed before ultrasound, then bilateral ultrasound of the nodal basins may not be necessary
[6] Refer to Jagsi, R., Mason, G., Overmoyer, B. A., Woodward, W. A., Badve, S., Schneider, R. J., . . . Miller, K. D. (2022). Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. *Breast Cancer Research and Treatment, 192*, 235-243. https://doi.org/10.1007/s10549-021-06434-x
[7] Perform nodal biopsy on the node which would have maximum impact on nodal staging and treatment. If both axillary and supraclavicular nodes appear suspicious, perform biopsy on supraclavicular node only.
[8] Skin punch not required. Consider MD Anderson approved breast biomarkers.
[9] For extensive skin involvement, consult plastic surgery for evaluation to assist with chest wall closure or immediate lymphatic reconstruction
[10] Consult Plastic Surgery for patients who are interested in having reconstructive surgery later and want to discuss plastic surgery prior to modified radical mastectomy
[11] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[12] Contact the clinical trial coordinator of the IBC registry at MD Anderson

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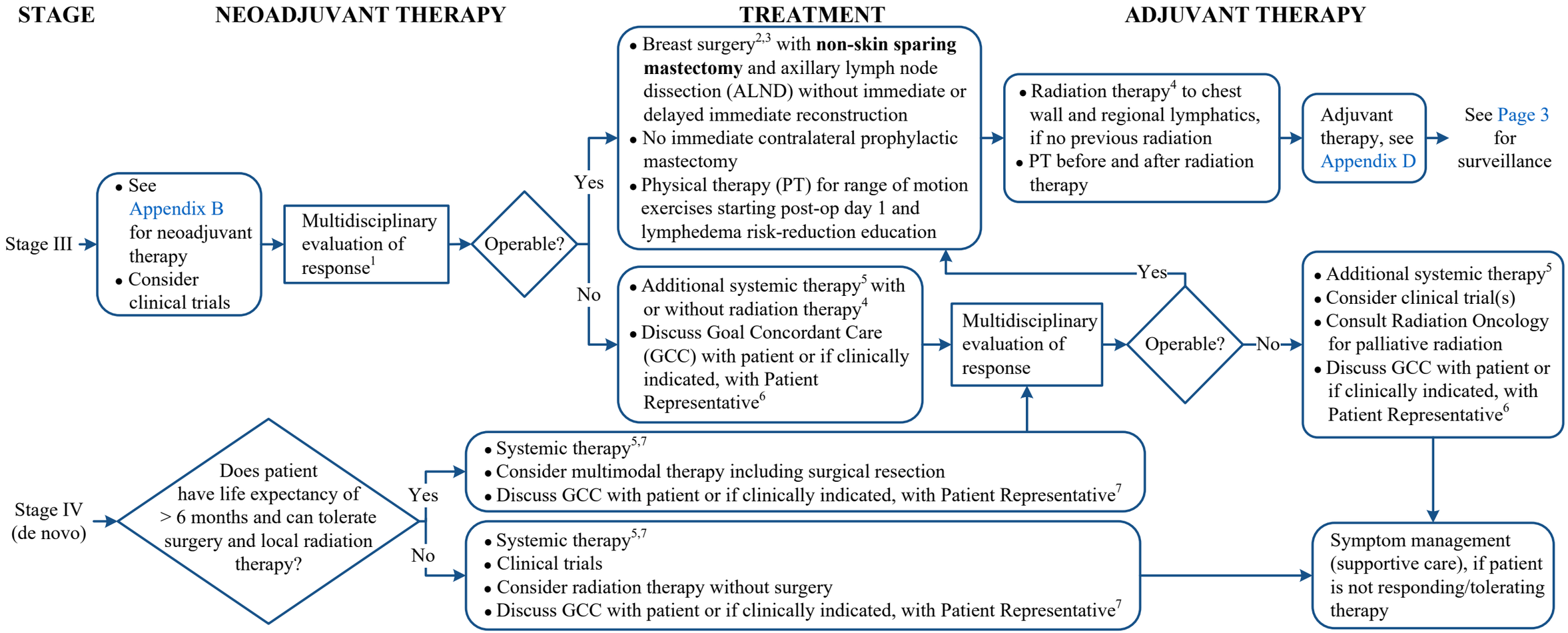
Note: Consider Clinical Trials as treatment options for eligible patients.



[1] Borderline resectable cases should be monitored closely and proceed to surgery if the tumor is progressing or the window for surgery and radiation therapy will be lost
[2] For extensive skin involvement, ensure that all grossly abnormal skin is resected. Plastic surgery assistance may be required with chest wall closure or immediate lymphatic reconstruction.
[3] Breast surgery is performed 4-6 weeks after neoadjuvant therapy
[4] See Appendix C: Principles of Radiation Therapy
[5] See Appendix E: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options
[6] 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).
[7] Next-generation sequencing (NGS) should be done for patients who eligible for systemic therapy

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

SURVEILLANCE

- Physical exam at least every 3 months for 2 years, every 6 months for 3 years, then annually
- Annual gynecologic exam, if receiving tamoxifen
- Imaging is guided based on patient complaints and physical examination findings
- 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 botox injections for radiation induced restricted range of motion unrelieved by physical therapy
- Consider referral to Plastic Surgery for autologous fat grafting to reduce radiation related fibrosis, delayed breast reconstruction, or for lymphedema surgery

→ See Page 4 for evaluation of local recurrence

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

EVALUATION FOR LOCAL RECURRENCE

Ipsilateral breast/chest wall recurrence or ipsilateral regional nodal recurrence with oligometastases or without diffuse metastases[1]

Biopsy to confirm recurrence with:
- If intact breast, bilateral diagnostic mammography
- MRI breast with and without contrast
- Ultrasound of bilateral nodal basins
- Body imaging for distant recurrence
- Biomarkers[2] of breast/chest wall recurrence or nodal recurrence (if no breast/chest wall recurrence)

- Early evaluation by multidisciplinary team
- Preoperative systemic therapy

TREATMENT FOR RECURRENCE

Breast intact?

Yes → Previous breast radiation therapy?

Yes → Modified radical mastectomy
- Refer to Principles of Radiation Therapy (see Appendix C)
- Consider Radiation Oncology consult[3]

No → Modified radical mastectomy with or without ALND **and**
- Radiation Oncology consult[3]

No → Resectable?

Yes → Consider neoadjuvant therapy[3,4]
- Wide local excision (WLE) with margin assessment

Previous chest wall radiation therapy?

Yes →
- Consider systemic therapy[4,5,6]
- Refer to Principles of Radiation Therapy (see Appendix C)
- Consider Radiation Oncology consult

No →
- Consider systemic therapy[4,5,6]
- Radiation Oncology consult
- Discuss GCC with patient or if clinically indicated, with Patient Representative[7]

No → Endocrine therapy[5] or HER2-directed therapy with or without chemotherapy[4]

Resectable?

Yes → Surgical resection with margin assessment[3]

No →
- Radiation therapy to chest wall and regional lymphatics, if no previous radiation[3]
- Discuss GCC with patient or if clinically indicated, with Patient Representative[7]

Persistent disease?

Yes →
- Consider additional systemic therapy[4,5,8]
- Surveillance[6] and endocrine therapy if hormone receptor positive[5]
- Consider chemotherapy[4,5,8]
- Discuss GCC with patient or if clinically indicated, with Patient Representative[7]

No → Surveillance[6] and endocrine therapy if hormone receptor positive[5]
- Consider chemotherapy[4,5,8]
- Discuss GCC with patient or if clinically indicated, with Patient Representative[7]

[1] For diffuse metastasis, consider clinical trials and see Breast Cancer – Metastatic Disease algorithm
[2] Consider MD Anderson approved breast biomarkers
[3] For isolated regional nodal recurrence, multidisciplinary review after systemic therapy for optimal local regional management
[4] See Appendix B: Neoadjuvant Systemic Therapy Options
[5] See Appendix D: Adjuvant Systemic Therapy Options
[6] Surveillance upon completion of all therapy, see Page 3
[7] 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 ACP note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
[8] See Appendix E: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

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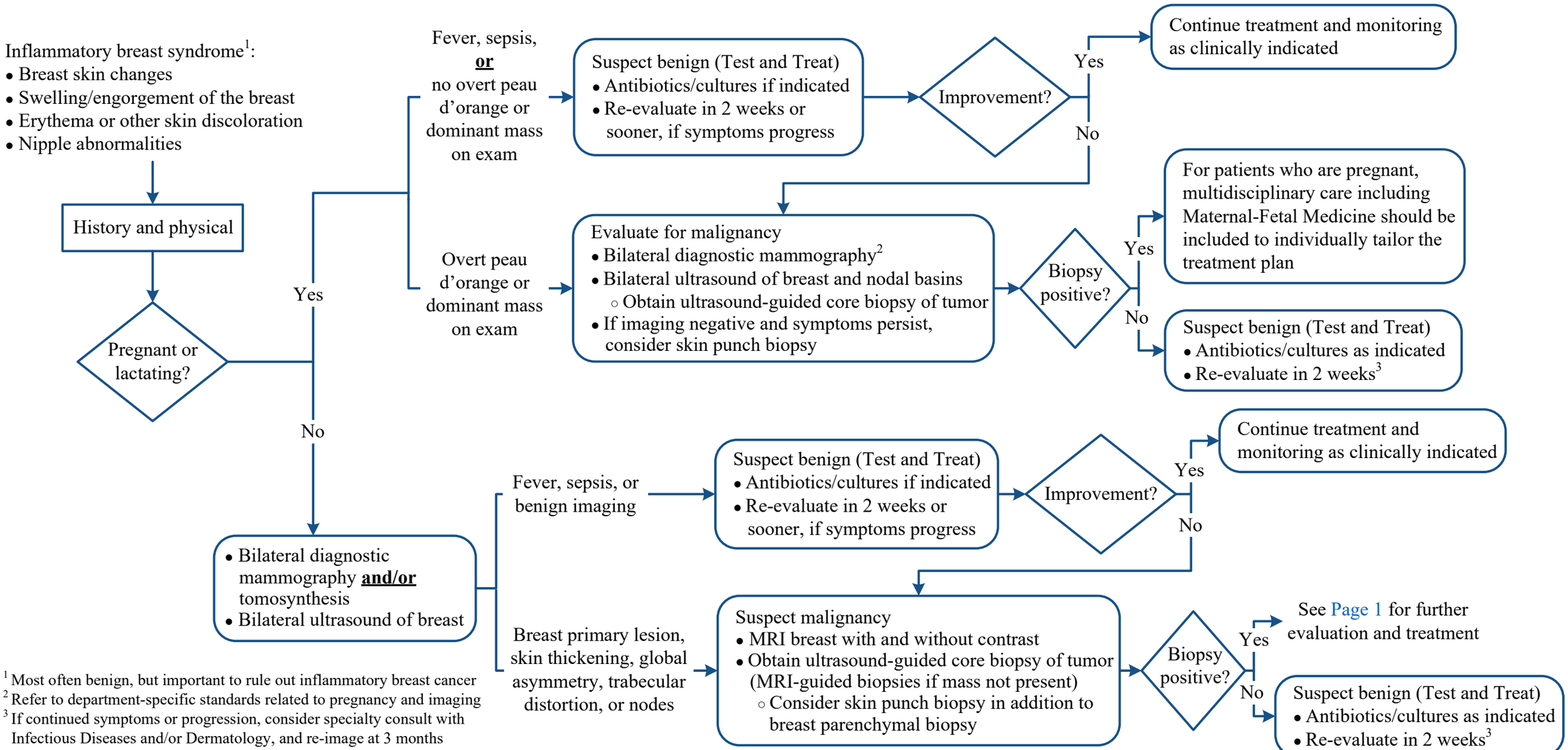
APPENDIX A: Undiagnosed Breast Cancer Evaluation



[1] Most often benign, but important to rule out inflammatory breast cancer
[2] Refer to department-specific standards related to pregnancy and imaging
[3] If continued symptoms or progression, consider specialty consult with Infectious Diseases and/or Dermatology, and re-image at 3 months

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APPENDIX B: Neoadjuvant Systemic Therapy Options[1]

Molecular Subtypes	First Line Therapy	Considerations
TNBC	Weekly paclitaxel for 12 doses or dose dense paclitaxel every 2 weeks for 4 cycles followed by or preceded by dose dense AC every 2 weeks or AC every 3 weeks **or** If no contraindications, weekly paclitaxel for 12 doses with carboplatin weekly for 12 weeks or every 3 weeks for 4 cycles followed by AC every 3 weeks for 4 cycles PLUS pembrolizumab 200 mg every 3 weeks to complete one year of treatment	Consider adding carboplatin to paclitaxel (only for first option)
ER+	Weekly paclitaxel for 12 doses or dose dense paclitaxel every 2 weeks for 4 cycles, followed by or preceded by dose dense AC every 2 weeks or AC every 3 weeks	
HER2+	AC (dose dense every 2 weeks or every 3 weeks for 4 cycles) for 4 cycles followed by THP every 3 weeks for 4 cycles **or** THP for every 3 weeks for 4 cycles followed by AC (dose dense for every 2 weeks or every 3 weeks for 4 cycles)	TCHP for 6 cycles as a second choice

Chemotherapy Regimen	Dose
AC	Doxorubicin (Adriamycin®) 60 mg/m^2 IV Cyclophosphamide 600 mg/m^2 IV
THP	Docetaxel 75 mg/m^2 IV Trastuzumab 8 mg/kg loading dose IV, followed by 6 mg/kg IV Pertuzumab 840 mg loading dose IV, followed by 420 mg maintenance dose IV
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 loading dose IV, followed by 420 mg maintenance dose IV

AC = doxorubicin and cyclophosphamide
TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab
THP = docetaxel, trastuzumab, pertuzumab
TNBC = triple negative breast cancer

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

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APPENDIX C: Principles of Radiation Therapy

General Principles

- Adjuvant radiation therapy should begin within 4 weeks after final surgical resection, when feasible
- Radiation therapy should be completed before or, as appropriate, concurrent with adjuvant systemic therapy (*e.g.,* pembrolizumab or HER2-directed therapy). In the setting of twice daily (BID) fractionation, consider holding concurrent systemic therapy during the second half of the treatment course with the development of subjectively excess acute toxicity.

Commonly used Radiation Prescriptions

Age > 45 years **and** pathologic complete response (pCR)	Daily (QD) fractionation: • 50 Gy in 25 daily fractions to the chest wall and regional lymph nodes (axilla, infraclavicular fossa (ICLV), supraclavicular fossa (SCV), and internal mammary chain (IMC) • 10 Gy in 5 daily fractions sequential boost to the chest wall flaps and unresected clinically involved lymph nodes with pCR
Age ≤ 45 years **or** no pCR	Twice daily (BID) fractionation: • 51 Gy in 34 twice daily fractions to the chest wall and regional lymph nodes (axilla, ICLV, SCV, and IMC) • 15 Gy in 10 twice daily fractions sequential boost to the chest wall flaps and unresected clinically involved lymph nodes Daily (QD) fractionation (for patients who decline BID fractionation): • 50 Gy in 25 daily fractions to the chest wall and regional lymph nodes (axilla, ICLV, SCV, and IMC) • 16 Gy in 8 daily fractions sequential boost to the chest wall flaps and unresected clinically involved lymph nodes with pCR

Treatment Planning

- 3-dimensional (3D) CT-based simulation and treatment planning should be performed utilizing adequate immobilization for reproducibility
- Wire markers are placed along any scars, drains, and anatomical boundaries to facilitate treatment planning
- 3D conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) may be utilized for both the primary treatment plan and/or the boosts, depending on clinical benefits, and should be strongly considered for cN3 disease
- In 3D-CRT plans using tangents with electron fields for the IMC, junctions between fields may be overlapped 3 mm to ensure the skin is not underdosed. This may subsequently be reduced or omitted after treatment plan review to decrease heterogeneity.

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APPENDIX C: Principles of Radiation Therapy - continued

Target Volume Delineation

- Initial cross-sectional diagnostic imaging (CT scan with IV contrast; PET scan) should be reviewed and fused to the CT simulation planning scan to assist with accurate target volume delineation of gross target volumes (GTVs) and clinical target volumes (CTVs)
- The Radiotherapy Comparative Effectiveness (RADCOMP) guidelines for target volume delineation of CTVs should be utilized for all IMRT/VMAT cases for patients with IBC
- CTVs will be subtracted from organs at risk (OARs), with attention to the thyroid and esophagus, as well as 3mm from the skin to create planning CTVs (pCTVs)
- CTVs and pCTVs should ensure volume(s) delineated for clinically involved unresected lymph nodes as visualized on cross-sectional diagnostic imaging prior to chemotherapy (pGTV_PreChemo_LN) are included, with a 1-2 cm margin expansion, edited for clinical areas at risk and constrained to the primary elective nodal pCTVs
- Planning treatment volumes (PTVs) will be expanded from delineated pCTVs for all target volumes and limited 3 mm from the skin, as directed below, when using IMRT/VMAT treatment planning
- Planning organ at risk volume (PRV) of the esophagus (PRV_Esophagus) should be created as a 3 mm expansion from the esophagus. The PTV_SCV (supraclavicular) will be subtracted from the PRV_Esophagus to facilitate esophageal constraints, ensuring coverage of the pre-chemotherapy GTVs of unresected lymph nodes (pGTV_PreChemo_LN) is not compromised.
- Boost volumes of unresected clinically involved lymph nodes (pCTV_PreChemo_LN) should include a 1-2 cm expansion, at minimum, of the pGTV_PreChemo_LN and limited to the primary pCTV nodal volume(s)

Chest wall	• The radiation fields/chest wall target volumes should include all skin determined to be clinically involved at diagnosis prior to chemotherapy plus a 3 cm margin (refer to medical photography obtained at diagnosis, if available) • The chest wall musculature should be included with or without the ribs per physician discretion • All drain sites should be included in the radiation fields/chest wall target volumes plus a 1 cm margin • Care must be taken to review the scar extent and ensure the medial field provides 3 cm of dosimetric cover beyond the scar, even if this involves treating the opposite breast
Grossly involved lymph nodes	Lymph nodes that were grossly involved at diagnosis as visualized on cross-sectional diagnostic imaging prior to chemotherapy should be delineated on the planning scan and edited for clinical areas at risk (pGTV_PreChemo_LN)
Uninvolved Nodal Volumes *CTV_Axilla* *CTV_SCV* *CTV_IMC*	• The undissected and dissected axillary basins, ICLV/axillary apex, SCLV (anterior and posterior basins), and IMC nodes within the first 3 intercostal spaces (at minimum) should be delineated as mandatory target volumes on the CT planning scan • The posterior neck nodes should be included in the SCV nodal target volume • If there is clinical involvement of internal mammary nodes at diagnosis, consider including the 4^{th} or even 5^{th} intercostal spaces of the IMC depending on initial node involvement and normal tissue constraints • The SCV nodal target volume should be contoured to above the cricoid cartilage for involvement of levels 1-2 of the axilla, the arytenoids for involvement of the ICLV, and to at least above the hyoid bone for SCV involvement (consider 3D historic boundary was the mastoid tip)
Boost Volumes *CW_Boost* *CTV_PreChemo_LN*	• Chest wall boosts should cover the surgical flaps (larger than a scar boost) • Adequate coverage of the medial chest wall beyond the scar should be ensured • Clinically involved unresected lymph nodes (pGTV_PreChemo_LN) will be expanded by a 1-2 cm margin, edited for clinical areas at risk and constrained to the primary elective nodal pCTVs to achieve the pCTV_PreChemo_LN • When boosting the ICLV or SCV, a composite plan should be developed during initial planning to ensure brachial plexus constraints are not exceeded

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APPENDIX C: Principles of Radiation Therapy - continued

Coverage Criteria and Organ Constraints

- Grossly involved lymph nodes prior to chemotherapy (pGTV_PreChemo_LN) that are unresected should receive, at minimum, 100% of the target dose (V100% > 100%)

Target Volume	Definition	Criteria	Optimal
pGTV_PreChemo_LN	Unresected grossly involved lymph nodes (pre-treatment) as delineated using fused cross-sectional diagnostic imaging (CT with contrast; PET/CT) and edited for clinical areas at risk	V100%	100%
pCTV_ChestWall	CTV, subtracted 3 mm from the skin	V98%	≥ 98%
pCTV_Axilla	CTV, subtracted 3 mm from the skin	V98%	≥ 98%
pCTV_IMC	CTV, subtracted 3 mm from the skin	V98%	≥ 98%
pCTV_SCV	CTV, subtracted 3 mm from the skin, ensuring no overlap with the thyroid or the esophagus	V98%	≥ 98%
pCTV_PreChemo_LN	pGTV_PreChemo_LN plus 1-2 cm margin expansion (at minimum, per physician discretion), edited for clinical areas at risk and constrained to the primary elective nodal pCTVs	V98%	≥ 98%
PTV_ChestWall	pCTV plus 5 mm expansion in all directions except posteriorly (3 mm), subtracted 3 mm from the skin	V95%	≥ 95%
PTV_Axilla	pCTV plus 5 mm expansion in all directions, subtracted 3 mm from the skin	V95%	≥ 95%
PTV_IMC	pCTV plus 5 mm expansion in all directions, subtracted 3 mm from the skin	V95%	≥ 95%
PTV_SCV	pCTV plus 5 mm expansion in all directions except medially (no expansion toward thyroid), subtracted 3 mm from the skin	V95%	≥ 95%
PTV_PreChemo_LN	pCTV_PreChemo_LN plus 5 mm expansion in all directions, limited to the PTV for the elective nodal volumes within the primary plan.	V95%	≥ 95%

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APPENDIX C: Principles of Radiation Therapy - continued

Coverage Criteria and Organ Constraints - continued

Organ at Risk	Criteria	Optimal	Acceptable
Lung_Ipsilateral	V 20 Gy	≤ 33%	N/A
	V 10 Gy	≤ 68%	
	Mean	≤ 20 Gy	
Lung_Contralateral	V 20 Gy	≤ 8%	
Heart	V 20 Gy	≤ 4%	
	V 10 Gy	≤ 15%	
	Mean	≤ 5 Gy	
Ventricle_Left	V 5 Gy	≤ 25%	
Left Anterior Descending Artery (LAD)	Max	≤ 25 Gy	
	V 15 Gy	≤ 10%	
Thyroid	Mean	≤ 20 Gy	ALARA
Esophagus	Max	≤ 30 Gy	≤ 45 Gy

Organ at Risk	Criteria	Optimal	Acceptable
BrachialPlexus_Ipsilateral[1]	Max	≤ 52 Gy	N/A
Breast_Contralateral	Mean	≤ 5 Gy	ALARA
Liver	Mean	≤ 10 Gy	N/A
Stomach	Mean	≤ 5 Gy	
CeliacPlexus_Gatroesophageal Junction (GEJ)	Max	≤ 10 Gy	
	Mean	≤ 3 Gy	
Spinal Cord	Max	≤ 20 Gy	
Parotid_Ipsilateral	Mean	≤ 26 Gy	
Submandibular_Ipsilateral	Mean	≤ 26 Gy	≤ 36 Gy
Parotid_Contralateral	Max	≤ 10 Gy	N/A
Submandibular_Contralateral	Max	≤ 10 Gy	
Larynx	Mean	≤ 20 Gy	≤ 30 Gy

ALARA = as low as reasonably achievable

[1] Primary Plan. If sequential ICLV or SCV boost is planned, a composite plan will be created with the following constraints: max ≤ 66 Gy, mean ≤ 63 Gy.

Principles of Re-irradiation

- Prior radiation therapy records, including digital information and communication in medicine (DICOM) files, should be obtained and carefully reviewed. A composite plan should be created including both the radiation dose previously received and the radiation dose planned to be delivered.
- Re-irradiation should be discouraged if prior radiation therapy was completed within the past 2 years or if definitive dose cannot be safely delivered

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APPENDIX D: Adjuvant Systemic Therapy Options

Molecular Subtypes[1]	First Line Therapy	Considerations
TNBC[2]	• No residual disease (pCR) ◦ BRCA negative or BRCA positive: Pembrolizumab 200 mg IV every 3 weeks for 9 cycles • Residual disease (non-pCR) ◦ BRCA negative: Concurrent pembrolizumab and capecitabine; if pembrolizumab contraindicated, capecitabine alone ◦ BRCA positive: Olaparib 300 mg PO twice daily for 1 year **or** concurrent olaparib with pembrolizumab **or** sequential olaparib followed by pembrolizumab	N/A
ER+	• No residual disease (pCR), BRCA negative or BRCA positive ◦ Premenopausal[3] at diagnosis - OFS plus AI[4,5] for 10 years[6] - Tamoxifen for 10 years[6] only if OFS and AI[4] not feasible ◦ Postmenopausal at diagnosis - AI[4,5] for 10 years[6] - Tamoxifen for 10 years[6] only if AI[4,5] not feasible ◦ For patients with no residual disease, consider adjuvant abemaciclib in high risk patients • Residual disease (non-pCR) ◦ BRCA negative: Endocrine therapy as above plus abemaciclib 150 mg PO twice daily for 2 years. ◦ BRCA positive: Endocrine therapy as above plus olaparib. Consider abemaciclib after olaparib completed.	• Premenopausal ◦ Consider OFS plus tamoxifen for patients who cannot tolerate AI • Postmenopausal ◦ Consider adjuvant bisphosphonate
HER2+	• No residual disease (pCR): Trastuzumab plus pertuzumab for 1 year • Residual disease (non-pCR): Adjuvant T-DM1 for 1 year	• For residual disease (non-pCR), recommend neratinib for 1 year after completion of T-DM1 • For no residual disease (pCR), recommend discussion about neratinib for 1 year

AI = aromatase inhibitor OFS = ovarian function suppression pCR = pathological complete response T-DM1 = ado-trastuzumab emtansine TNBC = triple negative breast cancer

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] Consider clinical trials in all tumor subtypes

[2] For patients with pCR, see Page 3 for surveillance

[3] Male patients should be treated similarly to premenopausal patients. Use of aromatase inhibitors or fulvestrant should be accompanied by androgen deprivation therapy (medical/surgical).

[4] 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.

[5] Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy

[6] Duration of endocrine therapy should be at least 5 years, and preferably 10 years

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APPENDIX E: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

Chemotherapy

Preferred single agents:

Anthracyclines	Taxanes	Anti-metabolites	Other microtubule inhibitors
• Pegylated liposomal doxorubicin	• Paclitaxel	• Capecitabine • Gemcitabine	• Vinorelbine • Eribulin

Other single agents:

• Docetaxel • Cisplatin • Ixabepilone • Carboplatin • Albumin-bound paclitaxel • Epirubicin • Sacituzumab govitecan-hziy[1]

Combination chemotherapy regimens:

- AC (doxorubicin and cyclophosphamide)
- CMF (cyclophosphamide, methotrexate, and fluorouracil)
- Gemcitabine and carboplatin
- EC (epirubicin and cyclophosphamide)
- Gemcitabine and paclitaxel
- Ixabepilone/capecitabine
- Docetaxel and capecitabine

HER2 Based Therapies

First-line regimens for HER2-positive disease[2]: (patients with trastuzumab naïve disease or those who recurred > 12 months after adjuvant trastuzumab)

• Pertuzumab plus trastuzumab and docetaxel • Pertuzumab plus trastuzumab and paclitaxel • T-DM1 (ado-trastuzumab emtansine)

Other options (not considered preferred first options):

- Trastuzumab with docetaxel
- Trastuzumab with paclitaxel with or without carboplatin
- Trastuzumab plus pertuzumab (if pertuzumab not previously given)
- Trastuzumab with vinorelbine
- Trastuzumab with capecitabine
- Tucatinib, capecitabine, and trastuzumab
- Fam-trastuzumab deruxtecan-nxki[3]

Second line regimens and beyond (including those listed under first line but not used)[2]:

- Lapatinib plus capecitabine
- Trastuzumab plus lapatinib without cytotoxic therapy
- Neratinib[4]
- Neratinib plus capecitabine
- Trastuzumab plus capecitabine
- Trastuzumab plus capecitabine plus tucatinib
- Trastuzumab plus other agent

[1] Indicated in patients with TNBC or ER positive metastatic disease
[2] After maximal benefit achieved with chemotherapy, consider continuous anti-HER2 therapy alone or pertuzumab plus trastuzumab, if ER or PR positive, in combination with appropriate hormonal therapy (does not apply to T-DM1 or fam-trastuzumab deruxtecan-nxki)
[3] Also indicated for HER2-low breast cancer
[4] ERBB2 mutations without over expression of HER2; If ER positive, add endocrine based therapy

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APPENDIX E: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options - continued

Endocrine Based Therapies

- Aromatase inhibitors (AI)
  - Anastrozole
  - Exemestane
  - Letrozole
  - Exemestane plus everolimus
  - AI with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
- Tamoxifen
- Estrogen (estradiol)
- Danazol
- Megestrol acetate
- Fulvestrant
  - Fulvestrant with AI
  - Fulvestrant with everolimus
  - Fulvestrant with alpelisib for *PIK3CA* mutation
  - Fulvestrant with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
- Abemaciclib single agent
- Elacestrant for *ESR1* mutation

BRCA-positive directed therapies:
- Olaparib or Talazoparib

Triple Negative Breast Cancer with PD-L1 expression:
- Pembrolizumab plus chemotherapy (gemcitabine with carboplatin **or** albumin bound paclitaxel)

Molecularly targeted agents along with *NTRK* fusion-directed:
- Larotrectinib and Entrectinib

MSI-H/dMMR-positive:
- Pembrolizumab

Total Mutation Burden-High (TMB-H: ≥ 10 muts/mb):
- Pembrolizumab

***RET*-fusion:**
- Selpercatinib

Bone-directed therapies:
- Zoledronic acid
- Denosumab

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PRINCIPLES OF INFLAMMATORY BREAST ONCOLOGIC SURGERY

Multidisciplinary Management of Inflammatory Breast Cancer

- Surgical management of breast cancer is an important aspect of curative intent therapy. Surgical decision-making is imbedded within the context of the multidisciplinary management of the breast oncology patient (both male and female).
- Patient participation in clinical trials when appropriate is strongly encouraged
- Breast surgery is performed 4-6 weeks after neoadjuvant chemotherapy
- Post-operative radiation therapy is administered 4 weeks after surgery

Diagnosis of Breast Malignancy

- Dedicated breast imaging at presentation should include bilateral diagnostic mammography, MRI breast with and without contrast, and bilateral nodal basin ultrasound to evaluate extent of disease
- Core needle biopsy is the preferred method of diagnosis of a palpable breast mass or a non-palpable breast imaging abnormality. Pathology should include biomarker assessment.
- FNA biopsy can be used for additional suspicious lesions in the ipsilateral breast to evaluate for multifocal/multi-centric disease and for diagnosis of metastases in suspicious regional nodes
- Placement of radiopaque clip marker with confirmation by imaging should be performed after needle biopsy
- Medical photography can be clinically useful to follow response and characterize extent of skin involvement
- Punch biopsy of the skin should be considered to document skin involvement
- The IBC Scoring System may be calculated to assist in diagnosing borderline cases

Clinical Staging of the Axilla

Bilateral axillary ultrasound and physical examination are recommended for clinical axillary staging in inflammatory breast cancer. Biopsy of suspicious axillary node(s) and placement of radiopaque clip marker if positive for metastasis is recommended.

Surgical Management

- Modified radical mastectomy (MRM) is standard of care in patients with IBC. MRM refers to total mastectomy with axillary level I/II dissection. Immediate breast reconstruction is contraindicated. Contralateral prophylactic surgery is not recommended.
- Consider referral to plastic surgery for immediate prophylactic lymphovenous bypass
- Referral to plastic surgery for delayed reconstruction and for possible lymphedema intervention is recommended
- Psychosocial and body image concerns should be addressed prior to surgery
- 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. In IBC, this includes care to include excision of all grossly involved skin. Reconstructive approaches may be warranted given the extent of skin involvement and excision.
- 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.

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PRINCIPLES OF INFLAMMATORY BREAST ONCOLOGIC SURGERY - continued

Surgical Management - continued

- 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

Surgical Management of the Axilla

- ALND (level I and II) is indicated in patients with biopsy proven clinically node positive disease and pathologic positive nodal involvement. Level III dissection may be considered in patients with level III residual disease after neoadjuvant chemotherapy.
- Axillary 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
- 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
- Evaluation by a physical therapist for improved range of motion and screening for lymphedema is recommended

Neoadjuvant Systemic Therapy

- Neoadjuvant systemic therapy is standard of care in patients with IBC
- 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 mammograms (if recurrence after breast conserving surgery), breast/chest wall and bilateral 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, and PET-CT is preferred to understand the extent of lymph node involvement
- Multimodality therapy is recommended including systemic neoadjuvant therapy, and surgical resection followed by systemic adjuvant therapy and radiation therapy

Stage IV Disease

- For patients who have a life expectancy of > 6 months and can tolerate systemic therapy and local radiation therapy, consider multimodal therapy including surgical resection
- 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 disease is also recommended.
- If localized stage IV to the contralateral axilla, consider contralateral ALND followed by radiation therapy

Special Considerations

Palliative mastectomy may be considered in patients with advanced local progression, with symptomatic fungating, and with bleeding tumors not responsive to systemic therapy

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