Breast Cancer – Inflammatory (IBC)

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

CLINICAL 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

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
- Bilateral breast and nodal ultrasound (include contralateral nodes even if negative contralateral breast)
- Bilateral breast MRI, if ultrasound and mammogram is not diagnostic
- Obtain ultrasound-guided core biopsy of tumor (MRI-guided biopsies if mass not present)
  - Consider skin punch biopsy in addition to breast parenchymal biopsy
- 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 or c disease is suspected (supraclavicular, infraclavicular), add CT neck to CT chest/ abdomen/pelvis with contrast and bone scan.
- FNA or core biopsy[1] of an index suspicious nodes, if not already performed
- Clip placement of positive axillary node (N1 disease, < 4 nodes) 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[2]:

- HER2 (human epidermal growth factor receptor) status
  - Germline BRCA testing for HER2 negative status
- ER, PR status
- Composite histologic grade
- Histologic type
- Lymphatic/vascular invasion

→

- Consider Plastic Surgery consult[3,4]
- Enroll in prospective lymphedema screening program
- Pre-operative lymphedema education
- Lifestyle risk assessment[5]
- IBC education
- Enroll in IBC registry[6]
- 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] 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.
[2] Skin punch not required. Consider MD Anderson approved breast biomarkers.
[3] For extensive skin involvement, consult plastic surgery for evaluation to assist with chest wall closure or immediate lymphatic reconstruction
[4] Consult Plastic Surgery for patients who are interested in having reconstructive surgery later and want to discuss plastic surgery prior to modified radical mastectomy
[5] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[6] Contact the clinical trial coordinator of the IBC registry at MD Anderson

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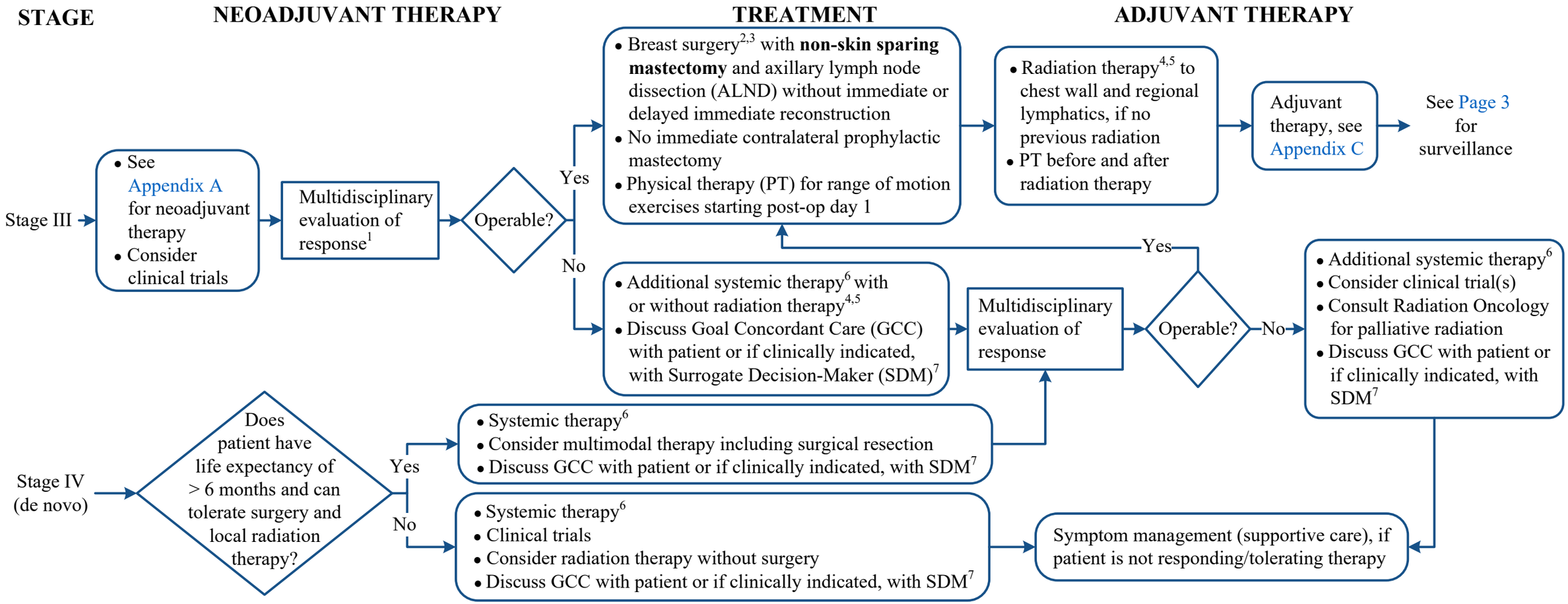
Breast Cancer – Inflammatory (IBC)

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] Evaluate breast and nodes for response to therapy:
- Minimal residual disease or pathologic complete response, age > 45 years and negative margins: Once daily radiation of 50 Gy (2 Gy/fraction)
- Significant residual disease, age ≤ 45 years or close or positive margins: Twice daily radiation of 51 Gy (1.5 Gy/fraction)
- Boost: Radiation to chest wall and involved undissected upfront regional nodes with 16 Gy daily **or** 15 Gy twice daily

[5] See Appendix B: Principles of Radiation Therapy

[6] See Appendix D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

[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 SDM 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 Goal Concordant Care home page (for internal use only).

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Breast Cancer – Inflammatory (IBC)

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
- Enroll in prospective lymphedema screening program, if not already enrolled
- 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

Breast Cancer – Inflammatory (IBC)

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 mammogram
- Ultrasound of bilateral breasts including regional 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

→ Breast intact?

- Yes → Previous breast radiation therapy?
  - Yes → Modified radical mastectomy; Refer to Principles of Radiation Therapy (see Appendix B); Consider Radiation Oncology consult
  - No → Modified radical mastectomy with or without ALND **and**; Radiation Oncology consult
- No → Resectable?
  - Yes → Consider neoadjuvant therapy[3]; Wide local excision (WLE) with margin assessment → Previous chest wall radiation therapy?
    - Yes → Consider systemic therapy[3,4,5]; Refer to Principles of Radiation Therapy (see Appendix B); Consider Radiation Oncology consult
    - No → Consider systemic therapy[3,4,5]; Radiation Oncology consult; Discuss GCC with patient or if clinically indicated, with SDM[6]
  - No → Endocrine therapy[4] or HER2-directed therapy with or without chemotherapy[3] → Resectable?
    - Yes → Surgical resection with margin assessment → Consider additional systemic therapy[3,4,7]
    - No → Radiation therapy to chest wall and regional lymphatics, if no previous radiation; Discuss GCC with patient or if clinically indicated, with SDM[6] → Persistent disease?
      - Yes → Consider additional systemic therapy[3,4,7]
      - No → Surveillance[5] and endocrine therapy if hormone receptor positive[4]; Consider chemotherapy[3,4,7]; Discuss GCC with patient or if clinically indicated, with SDM[6]

TREATMENT FOR RECURRENCE

[1] Consider clinical trial for diffuse metastasis
[2] Consider MD Anderson approved breast biomarkers
[3] See Appendix A: Neoadjuvant Chemotherapy Options
[4] See Appendix C: Adjuvant Chemotherapy Options
[5] Surveillance upon completion of all therapy, see Page 3
[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 SDM 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 Goal Concordant Care home page (for internal use only).
[7] See Appendix D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

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APPENDIX A: 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

[1] Refer to NCCN Guidelines for specific doses and number of cycles

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

APPENDIX B: Principles of Radiation Therapy

- Post-operative radiation therapy should be administered within 4 weeks after breast surgery when feasible
- Radiation therapy should be completed before adjuvant therapy
- All initially involved skin plus 3 cm margin should be included in radiation fields (refer to pre-chemotherapy photos, if available)
- Drain sites should be included in primary fields
- 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
- The chest wall, internal mammary chain (IMC) nodes in intercostal spaces 1-3 and undissected axillary apex/supraclavicular fossa are mandatory targets even if not grossly involved
- Initial cross sectional imaging must be reviewed and regional nodes transferred onto the planning scan to be targeted for boost planning
- In photon/electron plans junctions between fields are overlapped 3 mm to ensure skin is not underdosed
- Minimal IMC and regional nodal target coverage 90%
- Commonly used radiation regimens:
  - Age > 45 years **and** pCR: 50 Gy in 25 fractions to chest wall, infraclavicular, supraclavicular and IMC, 10 Gy/5 fx boost to chest wall and any N3 undissected nodal sites
  - Age ≤ 45 years **or** no pCR: 51 Gy twice daily to chest wall, infraclavicular, supraclavicular and IMC, 15 Gy/5 fx twice daily boost to chest wall and any N3 undissected nodal sites
- When boosting the infraclavicular or supraclavicular fossa in 3D plans, a composite is required during initial planning to ensure brachial plexus constraints are not exceeded
- Chest wall boosts should cover the surgical flaps (larger than a scar boost)

Principles of re-irradiation:

- Requires careful review of prior radiation therapy records
- Should be discouraged if prior radiation within 2 years
- Should be discouraged if definitive dose can not be safely delivered

APPENDIX C: 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 pembro contraindicated, capecitabine alone ◦ BRCA positive: Olaparib 300 mg PO twice daily for 1 year **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] for 10 years - Tamoxifen for 10 years only if OFS and AI[4] not feasible ◦ Postmenopausal at diagnosis - AI[4] for 10 years - Tamoxifen for 10 years only if AI[4] not feasible • 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

Notes:

- Longer durations of endocrine therapy (AI and tamoxifen) for > 5 years provide larger absolute benefit for higher risk cases (*e.g.*, node-positive, or stage III)
- 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 postmenopausal (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 or < 55 years old, consider verifying with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels. If definitive BSO with hysterectomy, verification with hormone levels is not indicated. Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy.

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

Chemotherapy

Preferred single agents:

Anthracyclines
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Docetaxel
- Cisplatin
- Ixabepilone
- Carboplatin
- Albumin-bound paclitaxel
- Epirubicin
- Sacituzumab govitecan-hziy

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[1]: (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
- Margetuximab-cmkb

Second line regimens and beyond (including those listed under first line but not used)[1]:
- Lapatinib plus capecitabine
- Trastuzumab plus lapatinib without cytotoxic therapy
- Neratinib plus capecitabine
- Trastuzumab plus capecitabine
- Trastuzumab plus capecitabine plus tucatinib
- Trastuzumab plus other agent

Endocrine Based Therapies

Endocrine based therapies:
- Aromatase inhibitors (AI)
  - Anastrozole
  - Letrozole
  - Exemestane
  - AI with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
  - Exemestane plus everolimus
- Tamoxifen
- Fulvestrant
  - Fulvestrant with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib)
  - Fulvestrant with alpelisib
  - Fulvestrant with AI
- Abemaciclib single agent
- Megestrol acetate
- Estrogen (estradiol)
- Danazol

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)

[1] 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)

PRINCIPLES OF INFLAMMATORY BREAST ONCOLOGIC SURGERY

Multidisciplinary management of invasive breast cancer

- Surgical management of breast cancer is an important aspect of curative intent therapy. Surgical decision-making is imbedded within the context of the multidisciplinary management of the breast oncology patient (both male and female).
- Patient participation in clinical trials when appropriate is strongly encouraged
- 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 mammograms and bilateral breast/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 should be utilized in patients who present with skin changes
- Punch biopsy of the skin should be considered to document skin involvement

Surgical management

- Modified radical mastectomy (MRM) is standard of care in patients with IBC. Immediate breast reconstruction is contraindicated. Contralateral prophylactic surgery is not recommended.
- 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

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 radiopaque clip marker if positive for metastasis is recommended.

Management of biopsy proven axillary disease

- 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.
- Evaluation by a physical therapist for improved range of motion and screening for lymphedema is recommended

Continued on next page

PRINCIPLES OF INFLAMMATORY BREAST ONCOLOGIC SURGERY - continued

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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