

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Breast Cancer (2020)

About the Guideline

- All recommendations in this guideline are considered appropriate.
- All recommendations are considered NCCN Category 2A unless otherwise indicated within the guideline.
- The NCCN Categories of Evidence are as follows:
 - Category 1: Based on high-level evidence with uniform NCCN consensus.
 - Category 2A: Based on lower-level evidence with uniform NCCN consensus.
 - Category 2B: Based on lower-level evidence with NCCN consensus.
 - Category 3: Based on any level of evidence with major disagreement among the panel that the intervention is appropriate.
- The NCCN Guideline Panel members included 31 medical doctors and three nonphysician members.

Overview

- Breast cancer is the most common malignancy in women and second leading cause of cancer deaths in women.
- Major risk factors include female gender and increased age (only 1% of breast cancers occur in men).
- Staging:
 - All breast cancer patients should be assigned a stage (clinical and pathologic).
 - Staging allows for the identification of all treatment options.
- This guideline provides updated guidelines for the management of carcinoma in situ, invasive breast cancer, Paget disease, Phyllodes tumor, invasive breast cancer, and breast cancer during pregnancy.

Key Clinical Considerations

Become familiar with the recommendations and best-practice statements provided in this guideline, especially if you work in an acute care setting.

Pathology Assessment

- The College of American Pathologists' protocols provide consistent and unambiguous pathology reporting guidelines that are essential in the analysis of breast cancer specimens.
- For ductal carcinoma in situ (DCIS): estrogen receptor (ER) status must be determined.
- For invasive breast cancer: both ER and progesterone receptor (PR) status is determined.
- For newly diagnosed invasive breast cancer and first recurrence: human epidermal growth factor receptor 2 (HER2) tumor status should be determined.

General Treatment Approach

- The treatment approach for breast cancer varies.
- Decisions about the type of treatment take into consideration the following factors:
 - Tumor histology
 - Clinical and pathologic characteristics of tumor

- Lymph node involvement
- Hormone receptor status
- HER2 status
- Presence of metastatic disease
- Comorbidities
- Age
- Menopausal status (in women)
- **Local disease:** surgery and/or radiation.
- **Systemic disease:**
 - Chemotherapy
 - Endocrine therapy
 - Biologic therapy
 - Or a combination of the three

Noninvasive Carcinomas (Stage 0)

- Ductal carcinoma in situ (DCIS)
 - Workup includes:
 - History and physical
 - Bilateral diagnostic mammography
 - Pathology review
 - ER status
 - Breast magnetic resonance imaging (MRI) for select patients when additional information is warranted
 - Genetic testing if the patient is at risk for hereditary breast cancer.
 - Treatment goal: to prevent progression to invasive breast cancer.
 - Surgery:
 - Lumpectomy, with or without whole breast radiation therapy (WBRT) to remove possible microscopic disease, with or without radiation boost to tumor site.
 - Mastectomy for widespread disease with possible sentinel lymph node biopsy performed as well.
 - Possible breast reconstruction.
 - Lumpectomy without lymph node surgery and partial breast radiation.
 - Lumpectomy without lymph node surgery or radiation.
 - Endocrine therapy: tamoxifen (premenopausal and postmenopausal women) or aromatase inhibitor (postmenopausal women younger than age 60) reduces the risk of ipsilateral breast cancer in ER-positive DCIS.
 - Surveillance and follow-up with an interval history and physical exam every 6 to 12 months for 5 years, then annually; a mammogram should be performed every 12 months.

Invasive Breast Cancer (Stage I, IIA, IIB, or IIIA)

- Workup includes:
 - History and physical
 - Bilateral diagnostic mammography
 - Breast ultrasonography
 - Breast MRI
 - Pathology review
 - ER/PR status and HER2 status

- Additional:
 - Genetic counseling
 - Fertility counseling
 - Distress assessment
 - Pregnancy test for women of childbearing age
- Laboratory and other diagnostic tests:
 - Complete blood count (CBC)
 - Liver function testing
 - Computerized tomography (CT) scan of the chest, abdomen, and pelvis as clinically indicated
 - Bone scan
 - Positron emission tomography (PET) scan for patients who present with locally advanced disease (T3, N1-3, M0)
- Treatment:
 - Lumpectomy with or without WBRT, *or*
 - Total mastectomy with surgical axillary staging and reconstruction
 - Adjuvant systemic therapy
 - Sentinel lymph node mapping and resection
 - Radiation therapy: whole breast, chest wall, regional nodal irradiation, accelerated partial breast irradiation

Breast Reconstruction

- Reconstruction is an option for women undergoing surgical treatment.
- Refer patients to a reconstructive plastic surgeon for education regarding options and timing.
- The type of reconstruction chosen should not interfere with tumor treatment.

Systemic Therapy (Stage I, IIA, IIB, or IIIA)

- Preoperative therapy
 - Can improve surgical outcomes.
 - Effectiveness depends upon the extent of disease and is not appropriate for all breast cancer patients.
 - Includes the following: chemotherapy, endocrine therapy, HER2-targeted therapy.
 - Tumor response should be routinely assessed during preoperative therapy.
- Systemic adjuvant therapy
 - The postsurgical treatment regimen depends on the individual's risk for recurrence.
 - Hormone receptor (HR) positive/HER2 negative—adjuvant endocrine therapy
 - HR negative/HER2 positive—one year of HER2-targeted therapy
 - HR negative/HER2 negative—consider capecetibine
 - HR positive/HER2 positive—endocrine therapy with up to one year of HER2-targeted therapy
- Adjuvant endocrine therapy
 - ER/PR status must be determined for all invasive breast cancers. The majority of hormone receptor-positive breast cancer patients should receive adjuvant endocrine therapy.
 - Postmenopausal women: tamoxifen.
 - Premenopausal women: tamoxifen, with or without ovarian suppression/ablation. Therapy can be extended with an aromatase inhibitor after the 5 years of treatment if

the patient becomes postmenopausal, **or** an aromatase inhibitor can be used with or without ovarian suppression/ablation.

- Tamoxifen: for patients with ER-positive breast cancer; given after chemotherapy in patients receiving both adjuvant chemotherapy and endocrine therapy; 5 years most beneficial.
- Adjuvant cytotoxic chemotherapy
 - Preferred regimens are as follows:
 - Dose-dense DOXOrubicin and cyclophosphamide (AC) followed by dose-dense PACLitaxel.
 - Dose-dense AC followed by every 2 weeks PACLitaxel.
 - DOCEtaxel with cyclophosphamide (TC).
 - If triple negative breast cancer and residual disease remains, consider capecitabine
 - Additional regimens/chemotherapy can include:
 - AC alone; AC followed by DOCEtaxel every 3 weeks, or weekly PACLitaxel.
 - EpiRUBicin and cyclophosphamide.
 - Cytoxan, methotrexate and fluorouracil.

Invasive Breast Cancer Stage III

- Workup includes:
 - History and physical
 - CBC
 - Liver function tests
 - Chest imaging
 - Bilateral diagnostic mammography
 - Breast ultrasonography
 - Pathology review
 - ER/PR status and HER2 status
- Additional:
 - Genetic counseling
 - Fertility counseling
 - Distress assessment
 - Pregnancy test for women of childbearing age
- Optional:
 - Breast MRI
 - Abdominal imaging
 - PET/CT scan if clinically indicated
- Operable locally advanced breast cancer (T3, N1, M0):
 - Confined to breast and regional lymph nodes.
- Inoperable, and locally advanced breast cancer (clinical stage IIIA, IIIB or IIIC):
 - Preoperative systemic therapy: anthracycline-based chemotherapy, with or without a taxane.
 - HER2 positive: include preoperative trastuzumab.
 - Surgery: total mastectomy with lymph node dissection (possible delayed breast reconstruction); lumpectomy and axillary dissection.
 - Chest wall, breast, and supraclavicular node irradiation. This treatment is warranted due to the high risk of recurrence.

- Adjuvant therapy: completion of preoperative chemotherapy with subsequent endocrine therapy and trastuzumab therapy (if applicable).

Posttherapy Follow-Up (Stages I, II, and III)

- History and physical exams 1 to 4 times per year for 5 years, then annually.
- Annual mammography.
 - For patients who have had breast-conserving surgery and radiation therapy, annual mammography is recommended, but annual screening should not begin until 6 to 12 months after completion of radiation.
- Yearly gynecologic exams for patients taking tamoxifen (intact uterus) related to the risk of endometrial cancer with usage.
- Symptom management for patients on adjuvant endocrine treatment.
- Lymphedema assessment, education, and management.
- Avoid breastfeeding during endocrine or chemotherapy treatment.
- Baseline and periodic bone density exam for patients on aromatase inhibitors and for patients who experience ovarian failure. Avoid the use of hormones to treat osteoporosis or osteopenia (bisphosphonates are the preferred intervention).
- Maintain exercise regimen, an active lifestyle, and ideal body weight.

Stage IV Metastatic or Recurrent Breast Cancer

- Workup includes:
 - History and physical
 - CBC
 - Liver function tests
 - Chest imaging
 - Bone scan and radiographs of any painful weight-bearing bones
 - CT or MRI of the abdomen
 - Biopsy documentation of first recurrence (if applicable)
- Discuss goals of therapy.
- For patients who present with metastatic disease or the first recurrence of disease, a biopsy is performed and ER/PR/HER2 status is repeated (for the recurrence).
 - Management of local disease includes the following:
 - Mastectomy patients with local recurrence: surgical resection of the recurrence and radiation to the chest wall and supraclavicular area (if patient did not receive radiation therapy in the past or can receive additional radiation safely). Radiation alone if the patient has unresectable chest wall disease.
 - Breast-conserving therapy patients: total mastectomy with axillary lymph node staging.
 - Systemic chemotherapy or endocrine therapy with minimal side effects may be used as treatment, but neither is curative.
 - Single agent chemotherapy: anthracyclines, taxanes, antimetabolites, or nontaxane microtubule inhibitors.
 - Combination therapy of chemotherapy and endocrine therapy may be considered.
 - HER2-targeted therapy (pertuzumab plus trastuzumab).
 - Consider endocrine therapy for patients with hormone receptor negative disease.
 - Bisphosphonates: offer to patients as supportive therapy for bone metastasis.

- Distant sites of recurrence:
 - Surgery, radiation, or regional chemotherapy (intrathecal) for brain metastases, leptomeningeal disease, choroid metastasis, pleural effusions, pericardial effusions, or spinal cord compression.
- Monitoring of metastatic disease:
 - Use of Response Evaluation Criteria in Solid Tumors (RECIST) and the World Health Organization (WHO) criteria for reporting response, stability, and disease progression. The same method of assessment should be consistently used.

Special Considerations

- Paget disease is a rare disease involving neoplastic cells in the epidermis of the nipple and areola. Tumors can also be present inside the same breast. These breast tumors are either DCIS or invasive breast cancer. If the biopsy is positive, a breast MRI is warranted to define disease extent.
 - Management: mastectomy or breast -conserving surgery following whole breast radiation, adjuvant chemotherapy, hormone therapy, and endocrine therapy.
- Phyllodes tumor is a rare tumor that can be benign, borderline, or malignant, and which can enlarge rapidly.
 - Treatment: local surgical excision, lumpectomy or partial mastectomy (full mastectomy if clear margins cannot be obtained).
- Inflammatory breast cancer (IBC)
 - Rare, aggressive form of breast cancer (1% to 6% in the United States).
 - Involves erythema and dermal edema (peau d'orange) of 1/3 or more of the skin of the breast.
 - Usually hormone receptor negative and HER2 positive.
 - Workup includes: history and physical, CBC, platelet count, diagnostic bilateral mammogram with possible ultrasound and MRI.
 - Treatment: combined approach, with initial treatment involving preoperative systemic therapy with anthracycline-based regimen with or without taxanes completed prior to mastectomy, and targeted therapy involving mastectomy, and radiation.
- Axillary breast cancer
 - Occult breast cancer with axillary metastasis.
 - Treatment is based on node involvement.
 - Treatment can include any combination of the following: mastectomy, systemic chemotherapy, endocrine therapy, and/or trastuzumab.
- Breast cancer during pregnancy
 - Breast cancer occurring concurrently during pregnancy is a rare event.
 - Diagnosis is often delayed due to the patient and physician not suspecting the occurrence.
 - Mammogram and ultrasound can be safely completed during pregnancy with proper shielding.
 - The most common surgical treatment is modified-radical mastectomy; however, breast-conserving surgery is an option if radiation can be postponed until the postpartum period.

Reference

National Comprehensive Cancer Network. (2020). NCCN clinical practice guidelines in oncology breast cancer, version 5.2020.