

Breast Cancer

About the Guideline

- The National Comprehensive Cancer Network (NCCN) Guideline Panel consists of 31 medical doctors and 3 nonphysician members.
- All recommendations in this guideline are considered appropriate.
 - Most of the recommendations are considered NCCN Category 2A (based on lower-level evidence with uniform NCCN consensus); all are considered appropriate.

Overview

- Breast cancer is the most frequently diagnosed cancer in the world with an estimated 250,000 Americans diagnosed with invasive breast cancer in 2016; it remains the leading cause of cancer-related death in women.
- The etiology of most breast cancers is unknown; however numerous risk factors have been established with female gender and increasing age as the greatest risks. Other risk factors include family history of breast cancer, genetic mutations and prolonged exposure to hormones.
- All breast cancer patients should be assigned a stage (clinical and pathologic) allowing for the identification of all treatment options and providing baseline prognostic information.

Key Recommendations

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 along with ER and PR status.

General treatment approach

- 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, and menopausal status (in women).
- Treatment approach for breast cancer varies:
 - Local disease: surgery and/or radiation therapy
 - Systemic disease: chemotherapy, endocrine or biologic therapies or a combination

Specific Treatment Recommendations

Pure noninvasive carcinomas (Stage 0)

- Includes both lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS)
 - LCIS:
 - History and physical, bilateral diagnostic mammography, and pathology review

- Classic LCIS requires no surgical treatment; it is managed by follow-up imaging and a physical examination (every 6 to 12 months)
- Patient counseling for risk of developing invasive breast cancer
- DCIS:
 - History and physical, bilateral diagnostic mammography, pathology review, ER status, magnetic resonance imaging (MRI) for select patients when additional information is warranted, and genetic counseling for patients at risk for hereditary breast cancer
 - Treatment goal is to prevent progression to invasive breast cancer.
 - Surgery:
 - Breast-conserving therapy (BCT): lumpectomy with or without whole breast radiation therapy (WBRT) (to remove possible microscopic disease), followed by endocrine therapy (to decrease the risk of recurrence)
 - Mastectomy (if disease involves 2 or more quadrants), with possible sentinel lymph node biopsy performed as well; possible breast reconstruction
 - 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/follow-up with interval history and physical exam (every 6 to 12 months for 5 years, then annually), mammogram every 12 months

Invasive breast cancer (stage I, IIA, IIB, or IIIA)

- Workup includes history and physical, bilateral diagnostic mammography, breast ultrasonography, pathology review, ER/PR status, HER2 status, genetic counseling, fertility counseling, and distress assessment.
- Complete blood count (CBC), liver function testing, computerized tomography (CT) scan of the chest, bone scan, positron emission tomography (PET) scan for patients who present with locally advanced disease (T3 N1-3 M0)
- Treatment:
 - Lumpectomy with or without whole breast radiation therapy (WBRT) or unilateral mastectomy
 - Adjuvant systemic therapy
 - Sentinel lymph node (SLN) mapping and resection
 - Radiation therapy: whole breast, chest wall, regional nodal irradiation, or accelerated partial breast irradiation (APBI)

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
 - 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
 - Postsurgical treatment; regimen depends on the individual's risk for recurrence
 - Breast cancer subtypes that impact disease-free and overall survival rates:
 - Luminal A: ER positive/HER2 negative
 - Luminal B: ER positive/HER2 negative
 - Basal: ER Negative/HER2 negative
 - HER2 positive
 - Tumors with characteristics similar to normal tissue
 - Gene-based assays predict the patient's prognosis and favorable response to systemic chemotherapy. A higher score indicates a higher risk. This can guide the systemic therapy decision by indicating whether there is a clear benefit to be gained from chemotherapy or not.
- Adjuvant endocrine therapy
 - ER/PR status must be determined in all invasive breast cancers. The majority of hormone receptor-positive breast cancer patients should receive adjuvant endocrine therapy.
 - Postmenopausal women: aromatase inhibitor and 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.
 - 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 weekly paclitaxel
 - Docetaxel with cyclophosphamide (TC)
 - Additional regimens/chemotherapy can include:
 - AC alone; AC followed by docetaxel every 3 weeks or weekly paclitaxel
 - Epirubicin and cyclophosphamide (EC)
 - Cytoxan, methotrexate and fluorouracil (CMF)
 - Targeted therapy: HER2 positive/node negative: trastuzumab (monoclonal antibody)

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
- Optional: breast MRI, abdominal imaging, PET/CT scan
- 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: warranted related to high risk of recurrence
 - Adjuvant therapy: completion of preoperative chemotherapy with subsequent endocrine therapy and trastuzumab therapy (if applicable)

Posttherapy follow-up (stages I-III)

- History and physical exams every 4 to 6 months for 5 years
- Annual mammography for patients that have had breast-conserving surgery and radiation therapy; 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
- Avoidance of hormonal birth control methods (for premenopausal women)
- Avoid breastfeeding during endocrine or chemotherapy treatment
- Baseline and periodic bone density exam for patients on aromatase inhibitors and patients who experience ovarian failure. Avoid the use of hormones to treat osteoporosis or osteopenia (bisphosphonates are the preferred intervention).
- Maintain exercise and 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).
- For patients who present with metastatic disease or first recurrence of disease, a biopsy is performed and ER/PR/HER2 status is repeated (for the recurrence).
 - Management of local disease:
 - 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 (BCT) 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, 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. Same method of assessment should be consistently used.

Special considerations

- Paget's 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 ductal carcinoma in situ or invasive breast cancer. If the biopsy is positive, a breast MRI is warranted to define disease extent.
 - Management: mastectomy or breast-conserving surgery, 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)
- Breast cancer during pregnancy is an infrequent clinical event; most often ALN-positive with poorly differentiated and larger primary tumor, frequently ER/PR negative, with 30% HER2 positive.
 - Evaluation: physical examination, mammogram with abdominal shielding, breast and regional node ultrasound, core needle biopsy
 - Treatment: local and systemic therapy are similar to that recommended in non-pregnancy associated breast cancer; however, the choice and timing of therapies is different.
 - Radiation should not be administered during any time of pregnancy
 - Chemotherapy should not be given during the first trimester
 - Mastectomy or breast-conserving surgery with delayed radiation
- 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)
- 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.

Reference:

National Comprehensive Cancer Network. (2018). NCCN clinical practice guidelines in oncology breast cancer, version 1.2018.

Link to Practice Guideline:

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf