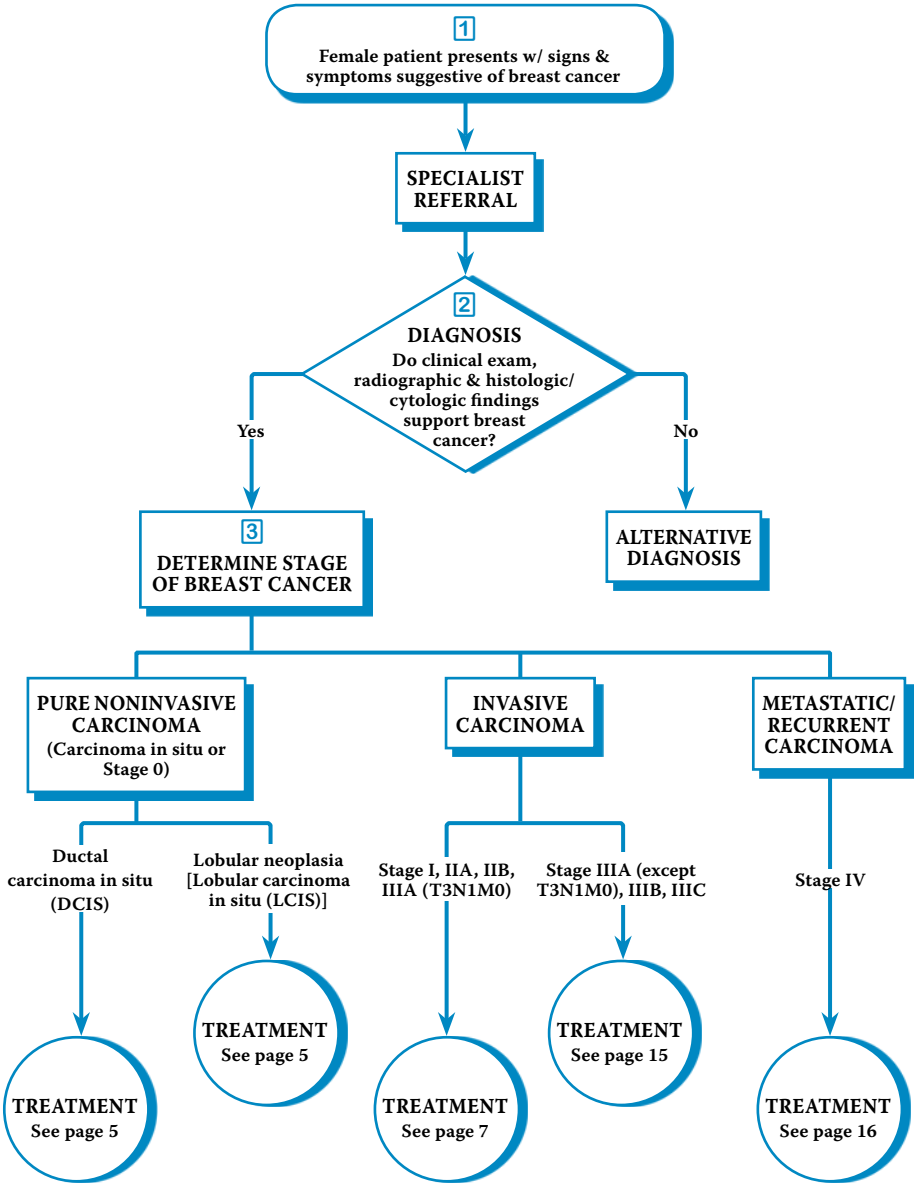
Breast Cancer (1 of 34)



1 BREAST CANCER

Signs & Symptoms
- Presence of breast nodule, mass, or abscess
  - Most common symptom of breast cancer is a new lump or mass in the breast
  - Painless, hard, & irregular mass is more likely to be cancerous, but can also be tender, soft, rounded, or painful
- Breast pain or nipple pain
- Nipple discharge
- Nipple retraction
- Presence of breast skin changes (eg peau d' orange, nipple excoriation, scaling, inflammation, skin tethering, ulceration, abscess)

Risk Factors
- History of breast cancer
  - Previous history of breast cancer has an increased risk of developing new primary breast cancer
    - History of invasive breast cancer, lobular neoplasia [formerly called lobular carcinoma in situ (LCIS)] & ductal carcinoma in situ (DCIS) have the highest risk
  - Breast carcinoma in situ can develop into invasive breast cancer
- Confirmed biopsy of benign proliferative breast disease
  - Breast tissue biopsy showing proliferative disease w/ & w/o atypical cells has an elevated risk of developing breast cancer
    - Patients w/ benign breast disease that presents w/ atypical hyperplasia carry the highest risk of developing cancer
- History of high-dose radiation exposure
  - Multiple exposures of therapeutic radiation to the chest for cancer at an early age (<20 yrs old) increase the risk of breast cancer
  - Contralateral breast cancer has been shown to develop after high-dose radiation exposure
  - Patients w/ Hodgkin's disease receiving radiotherapy at high doses are also at risk
- Reproductive factors
  - Nulliparity or first full-term pregnancy at age >30 yrs
    - Breastfeeding for >12 mths is protective against breast cancer
  - Menarche at age <12 yrs & menopause at age >55 yrs
  - Oral contraceptive use before the first full-term pregnancy, combination hormone replacement therapy, & long-term use of unopposed estrogen for >15 yrs by hysterectomized women have mild increased risk for breast cancer
    - Use of low-dose preparations poses a lower risk
- Advanced age
  - Risk increases from 40 yrs old for premenopausal women & 50 yrs old for postmenopausal women
- Family history of breast cancer
  - Increased risk in women w/ breast cancer among young first-degree relatives
    - Sister has a higher risk than a mother
  - Carriers of BRCA1 & BRCA2 genetic mutations are also at high risk
    - Women w/ these have increased risk of developing other cancers like ovarian cancer
- Breast density
  - Higher breast density has increased risk
- Lifestyle
  - Body mass index of >25 has an increased risk of developing breast cancer w/ higher death rate
    - 7 hrs/wk of moderate to vigorous exercise was shown to be inversely related to breast cancer development
  - Alcohol consumption (eg beer) of >10 g/day especially in postmenopausal women has increased risk for invasive breast cancer

2 DIAGNOSIS

Triple Assessment
- Established method to diagnose breast cancer
- Consists of clinical evaluation, imaging (ie mammography &/or ultrasound) & pathology (histology &/or cytology)

Criteria for Early Referral
- Women >40 yrs old complaining of breast lump
- Women at any age that has a lump >3 cm in diameter
- Presence of clinical signs of malignancy

Clinical Evaluation
- Includes complete medical history & physical examination

Medical History
- Ask for symptoms such as breast pain or presence of a new mass in the breast
- Assess risk factors for breast cancer

Physical Exam
- Complete breast examination
  - Inspection & palpation of the breasts should be done in upright & supine positions to determine subtle shape or contour changes in the breasts
  - Determine the presence of palpable lump or mass & its characteristics (eg location, size, texture, mobility, presence of asymmetric thickening or nodularity, retraction, nipple discharge, & skin changes)
  - Assess for axillary, supraclavicular & internal mammary lymph nodes, & other organs for metastatic disease
- In patients w/ nipple discharge w/o a palpable mass, evaluate the character of discharge for other causes

Imaging Procedures

Mammography
- Done bilaterally, detects clinically occult breast lesions
- Recommended screening method for women 50-74 yrs old every 1-2 yrs
- Not done routinely as screening method in low- & moderate-risk women ages 40-49 yrs but should not be denied in women who would like to undergo the procedure
  - Some have recommended annual mammogram in women starting at age 40 yrs

2 DIAGNOSIS (CONT'D)

Mammography (Cont'd)
- Preferred initial evaluation for high-risk women starting at age ≥30 yrs
  - Screening w/ both mammography & MRI provides more sensitivity than mammography alone
- Further evaluation is necessary after bilateral mammography

Ultrasound
- Preferred initial test for women age <30 yrs
- Used as an adjunct to mammography
- Determines the nature of the mass, whether fluid-filled or solid tissue, & assesses regional lymph nodes (LNs)
- May be useful in patients under 35 yrs old w/ focal breast disease

Magnetic Resonance Imaging (MRI)
- May be used in patients w/ metastatic deposits in axillary LNs where primary cancer has not been identified
- Should be considered in cases where other imaging procedures have been inconclusive or unreliable such as invasive lobular cancer, suspicion of multicentricity, genetic high risk, patients w/ breast implants or foreign bodies, diagnosis of recurrence, follow-up after neoadjuvant therapy, or in patients w/ dense breasts
- Not recommended in women w/ invasive breast cancer, lobular neoplasia, DCIS, & atypical hyperplasia

Bone Scan
- Recommended in patients complaining of bone pains, w/ elevated alkaline phosphatase (ALP) & w/ advanced breast cancer

Computed Tomography (CT) Scan
- Should be performed in patients w/ clinically advanced breast cancer to evaluate the possibility of metastases to other organs

Histologic/Cytologic Tests
- Breast tissue biopsy is recommended if mammogram &/or ultrasound findings are suspicious or highly suggestive of malignancy
- Fine needle aspiration (FNA) biopsy, core needle biopsy, or surgical (excisional) biopsy are types of needle biopsies used in diagnosing breast carcinoma

Fine Needle Aspiration (FNA) Cytology
- Initial method of pathological evaluation for palpable breast lumps
- Usually done in clinically positive axillary LN especially in large breast tumors
  - Ultrasound-guided FNA can be performed in nonpalpable lesions
- Minimally invasive method w/ low cost but needs a pathologist w/ specific expertise in test result interpretation & performing a follow-up tissue biopsy when atypia or malignancy is seen

Core Needle Biopsy
- Also called percutaneous core breast biopsy which can be performed under imaging guidance
  - May also be done under vacuum assistance which collects adequate tissue from a breast lesion w/o the need for multiple needle insertions
- Used as a complement for pathological diagnosis if FNA cytology is equivocal
- Preferred method of tissue biopsy if there is suspicious or indeterminate solid lesion detected by ultrasound
- Has higher accuracy over FNA when the mass is nonpalpable & has capability to obtain sufficient tissue sample sizes which eliminates the need for a follow-up biopsy to confirm malignancy

Surgical or Excisional Biopsy
- Gold standard of diagnosis w/ almost 100% sensitivity
- Recommended following diagnosis by core biopsy of an indeterminate lesion, atypical hyperplasia, lobular neoplasia, or a benign & image-discordant lesion
- Provides larger tissue samples but is a more invasive method than a core needle biopsy & also requires needle localization in a nonpalpable mass
- Sentinel lymph node biopsy
  - Preferred method of axillary LN staging if there is an experienced sentinel node team & if the patient is an appropriate candidate for sentinel LN biopsy
  - May be done in clinically negative axillary node in large breast tumors

Histologic Diagnosis

Carcinoma in Situ
- Cancer cells confined to the lobules or ducts w/o spread into surrounding tissues in the breast or to other organs in the body
- Includes lobular neoplasia & DCIS

Invasive Breast Cancer
- Most common breast cancer
- Cancer cells infiltrating the interlobular stroma
- Includes invasive ductal carcinoma, invasive lobular neoplasia, mixed tumors, medullary cancer, metaplastic tumors, inflammatory breast cancer, colloid carcinoma, tubular carcinoma
  - Colloid & tubular carcinoma are good prognosis cell types which are usually HER2 negative

Other Tests
- CBC, liver & renal function tests, alkaline phosphatase, calcium, liver ultrasound, & chest X-ray are recommended especially in patients w/ invasive breast carcinoma or advanced breast cancer

Tumor Tests
- Include tests for hormone receptors [eg estrogen receptor (ER), progesterone receptor (PR)] & human epidermal growth factor receptor 2 or HER2/neu
  - Perform HER2 testing on all newly diagnosed patients w/ primary or metastatic breast cancer using either immunohistochemistry (IHC) assay or in situ hybridization (ISH) assay to help guide decision regarding HER2-targeted therapy
    - Helps in accurately identifying patients who would benefit from HER2-targeted treatment & thereby preventing unnecessary side effects & cost of therapy

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)
- Consider 21-gene RT-PCR assay for estimating the probability of tumor recurrence

3 STAGING

- Determines the extent of cancer upon diagnosis
- Important factor in the choice of treatment & provides information about the prognosis of the disease
- Since asymptomatic metastases are rare, routine staging assessment is for local regional disease

Tumor, Nodes & Metastases (TNM) System

- Developed by the American Joint Committee on Cancer & Union Internationale Contre le Cancer

Staging

Stage 0
- Tis N0 M0
  - Carcinoma in situ, may either be ductal or lobular carcinoma or Paget's disease of the nipple w/o tumor; no regional LN metastasis & distant organ metastasis

Stage IA
- T1 N0 M0
  - Tumor size is ≤2 cm in widest dimension, no regional LN metastasis, no distant organ metastasis

Stage IB
- T0 N1mi M0
  - No evidence of primary tumor or distant organ metastasis, w/ metastasis to movable ipsilateral axillary LN that is >0.2 mm but ≤2 mm in widest dimension
- T1 N1mi M0
  - Tumor size is ≤2 cm in widest dimension, w/ metastasis to movable ipsilateral axillary LN that is >0.2 mm but ≤2 mm in widest dimension, no distant organ metastasis

Stage IIA
- T0 N1 M0
  - No evidence of primary tumor, w/ metastasis to movable ipsilateral axillary LN that is >2 mm in widest dimension, no distant organ metastasis
- T1 N1 M0
  - Tumor size is ≤2 cm in greatest dimension, w/ metastasis to movable ipsilateral axillary LN that is >2 mm in widest dimension, no distant metastasis
- T2 N0 M0
  - Tumor size is >2 cm but not >5 cm in widest dimension, no regional LN metastasis, no distant metastasis

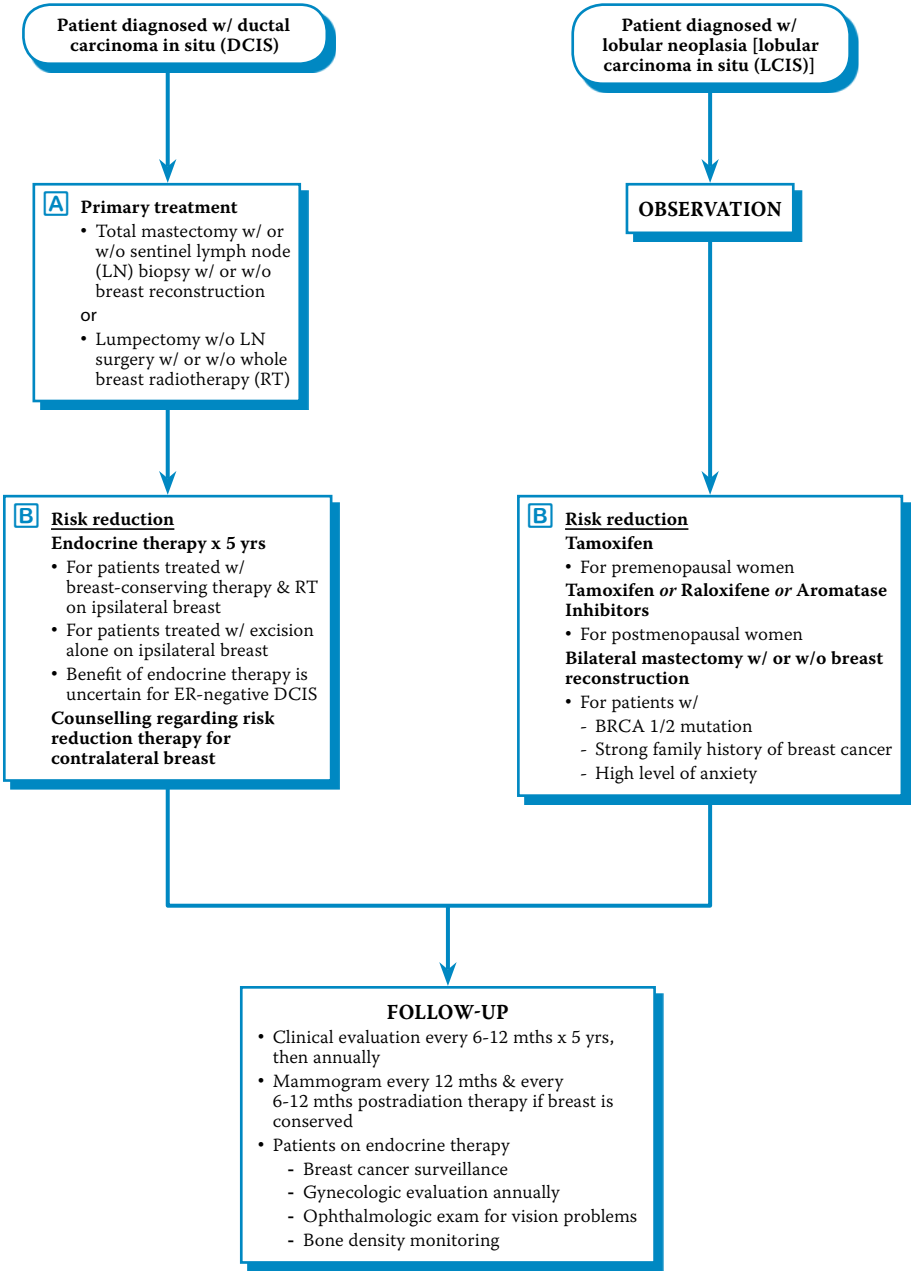
IIB
- T2 N1 M0
  - Tumor size is >2 cm but not >5 cm in greatest dimension, w/ metastasis to ipsilateral axillary LN that is movable, no distant metastasis
- T3 N0 M0
  - Tumor size is >5 cm in widest dimension, no regional LN metastasis, no distant metastasis

Stage IIIA
- T0 N2 M0
  - No evidence of primary tumor or distant organ metastasis; metastasis to ipsilateral axillary node(s) fixed or matted, or metastasis to ipsilateral internal mammary LN as detected by imaging studies, clinical assessment or grossly visible pathologically in the absence of clinically evident axillary LN metastasis
- T1 N2 M0
  - Tumor size is ≤2 cm in widest dimension; metastasis to ipsilateral axillary node(s) fixed or matted, or metastasis to ipsilateral internal mammary LN as detected by imaging studies, clinical assessment or grossly visible pathologically in the absence of clinically evident axillary LN metastasis; no distant metastasis
- T2 N2 M0
  - Tumor size is >2 cm but not >5 cm in greatest dimension; metastasis to ipsilateral axillary node(s) fixed or matted, or metastasis to ipsilateral internal mammary LN as detected by imaging studies, clinical assessment or grossly visible pathologically in the absence of clinically evident axillary LN metastasis; no distant organ metastasis
- T3 N1 M0
  - Tumor size is >5 cm in greatest dimension, w/ metastasis to movable ipsilateral axillary LN, no distant metastasis
- T3 N2 M0
  - Tumor size is >5 cm in greatest dimension; metastasis to ipsilateral axillary node(s) fixed or matted, or spread to ipsilateral internal mammary LN as detected by imaging studies, clinical assessment or grossly visible pathologically in the absence of clinically evident axillary LN metastasis; no distant metastasis

IIIB
- T4 N0 M0
  - Tumor of any size w/ direct extension to chest wall (eg ribs, intercostal muscles & serratus anterior muscle) or skin; no regional LN metastasis
- T4 N1 M0
  - Tumor of any size w/ direct extension to chest wall (eg ribs, intercostal muscles & serratus anterior muscle) or skin; metastasis to movable ipsilateral axillary LN
- T4 N2 M0
  - Tumor of any size w/ direct extension to chest wall (eg ribs, intercostal muscles & serratus anterior muscle) or skin; metastasis in ipsilateral level I, II axillary LN that are clinically fixed or matted; or in clinically identifiable ipsilateral internal mammary nodes in the absence of clinically evident axillary LN metastases

IIIC
- Any T N3 M0
  - Carcinoma in situ or tumor of any size w/ or w/o direct extension to chest wall or skin; metastasis to ipsilateral infraclavicular LN w/ or w/o axillary node involvement, or spread to ipsilateral internal mammary LN as detected by imaging studies, clinical assessment or grossly visible pathologically in the presence of clinically evident axillary LN metastasis; or metastasis in ipsilateral supraclavicular LN w/ or w/o axillary or internal mammary node involvement; no distant metastasis

Stage IV
- Any T Any N M1
  - Carcinoma in situ or tumor of any size w/ or w/o direct extension to chest wall or skin; w/ or w/o regional LN metastasis; w/ distant organ metastasis



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A PRIMARY TREATMENT FOR DUCTAL CARCINOMA IN SITU

- Patients w/ breast cancer in 1 area w/ positive margins after complete surgical excision are advised to undergo either total mastectomy or lumpectomy

Lumpectomy

- Associated w/ high recurrence rate
- RT may be offered in patients who are treated w/ lumpectomy
  - Several trials support the findings that lumpectomy w/ RT reduce recurrent DCIS & invasive disease in ipsilateral breast
- Sentinel node biopsy may be done
- Mammogram is advised postlumpectomy to ensure complete removal of the tumor

Total Mastectomy

- Associated w/ near-total avoidance of recurrence in 3-20 yrs
- Recommended in widespread DCIS w/ involvement of ≥2 areas & when there is persistent marginal involvement even after repeat surgery
- May not require post-op radiation unless the carcinoma is at the margin of the mastectomy
- Sentinel node biopsy may be done

RISK CATEGORIES FOR OPERATED BREAST CANCER

Low Risk

- Negative LN ***plus all*** of the following:
  - ≥35 yrs of age
  - Pathological tumor size (pT) of ≤2 cm
  - Absence of HER2/neu gene overexpression & amplification
  - No extensive peritumoral vascular invasion
  - Expression of ER &/or PR
  - Histologic &/or nuclear grade 1

Intermediate Risk

- Negative LN ***plus at least 1*** of the following:
  - <35 yrs of age
  - pT >2 cm
  - Histologic &/or nuclear grade 2-3
  - Extensive peritumoral vascular invasion
  - Absence of ER & PR expression
  - Presence of HER2/neu gene overexpression or amplification
  - Positive LN (1-3 nodes) & HER2 negative

High Risk

- Positive LN (1-3 nodes) & HERs overexpression, ***or***
- Positive LN (≥4 nodes)

B RISK REDUCTION FOR CARCINOMA IN SITU

Tamoxifen

- Competitively binds to cytoplasmic ER in breast, uterus, vagina, anterior pituitary & tumors containing high levels of ER
  - Competitive binding protects against development of breast cancer
- Decreases breast cancer risk in healthy premenopausal & postmenopausal women ≥35 yrs old
- More effective risk reduction agent for most menopausal women who want a non-surgical risk reduction therapy but has more toxic effects
- May be considered as an adjuvant therapy in DCIS patients who underwent breast conservation therapy especially in ER-positive DCIS; benefit of Tamoxifen in ER-negative DCIS is uncertain
  - Reduces the risk of cancer recurrence on the ipsilateral breast
- May be considered as risk reduction therapy in DCIS patients treated w/ mastectomy
  - Reduces the development of contralateral 2nd primary breast carcinoma
- Studies have shown that Tamoxifen can reduce the risk of invasive breast cancer in premenopausal & postmenopausal patients
  - Used in ER-positive tumor
  - Aromatase inhibitor may be of advantage in postmenopausal patients <60 yr old or w/ thromboembolism problems
- Advised to be taken for 5 yrs

Raloxifene

- Long-term use was shown to be less effective but a safer risk reduction agent compared to Tamoxifen in postmenopausal women

Surgery

- Preventive bilateral mastectomy may be an alternative for patients at high risk of developing invasive breast cancer

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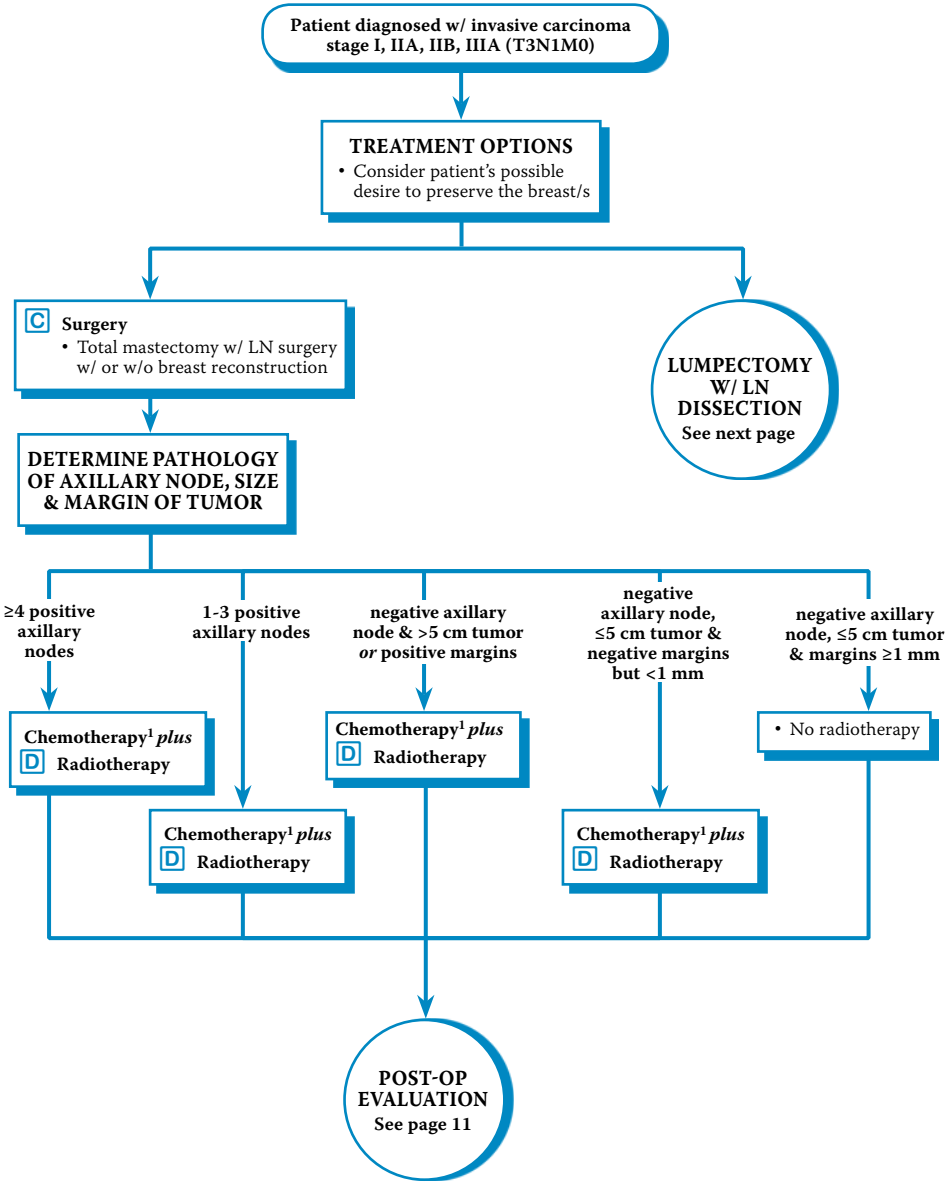
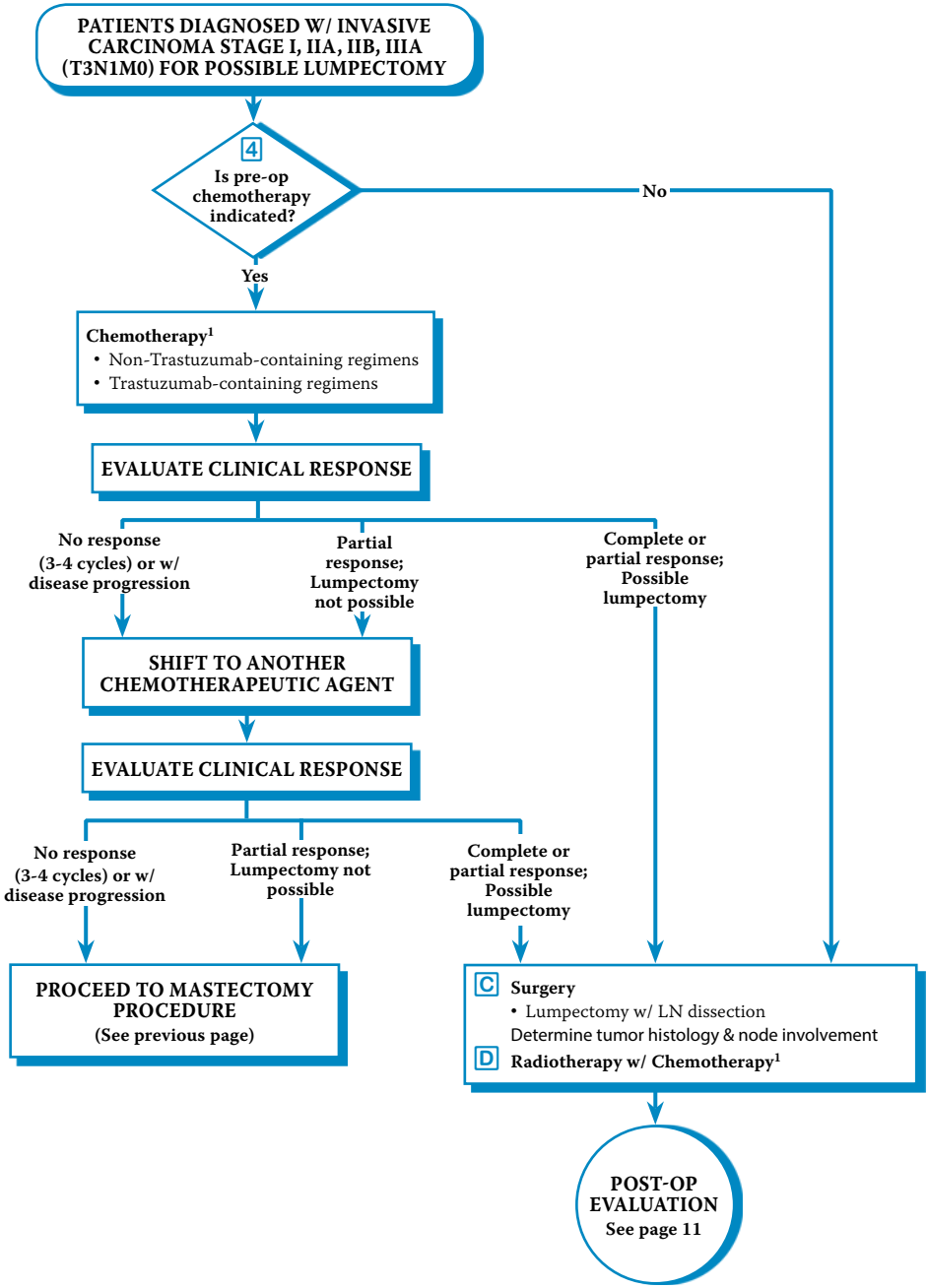


[1]For representative chemotherapeutic agents/combinations, please see page 14



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4 PREOPERATIVE CHEMOTHERAPY

- All chemotherapy administration before surgery is preferred
  - Modalities used in adjuvant therapy may also be used eg endocrine & targeted therapy
- Purpose is to reduce tumor size which allows complete removal of the tumor w/ less extensive surgery
- Can predict how the cancer cells respond to chemotherapeutic drugs
- Considered in women w/ large clinical stage IIA, IIB, & T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size & those who wish to undergo breast-conserving therapy
- Indications:
  - Tumor size >2 cm (T2, T3)
  - Cancer does not involve the surrounding skin or chest wall
  - LN enlarged but movable
- Endocrine therapy alone, ie Tamoxifen or aromatase inhibitor (for postmenopausal women; administered w/ ovarian suppression to premenopausal women) may be given in hormone receptor-positive disease
- Patients w/ HER2-positive tumors should be treated w/ pre-op chemotherapy incorporating Trastuzumab for at least 9 wks

C SURGERY

Breast-conserving Surgery

- Local treatment of choice for majority of early-stage invasive breast cancer
- Purpose is to provide a pathologically negative margin of resection
  - Image-detectable markers are placed during core biopsy for tumor bed demarcation for surgical management post chemotherapy
  - In cases where there is a positive margin, the option is to re-excise or perform mastectomy to achieve a negative margin
- Radiation is usually done after breast-conserving surgery
- Survival rates are similar to mastectomy alone for stage I or II treated w/ lumpectomy & RT & in patients w/ DCIS treated w/ breast-conserving surgery & RT
- Absolute contraindications for breast-conserving surgery requiring RT:
  - RT during pregnancy
  - Pathologic margins that are diffusely positive
  - Suspicious or malignant-appearing microcalcifications that are disseminated throughout the breast
  - Extensive disease that cannot be incorporated by local excision through a single incision that may result in negative margins w/ acceptable cosmetic result
- Relative contraindications:
  - Tumor size >5 cm
  - Positive pathologic margin
  - Prior chest wall or breast radiation therapy
  - Active connective tissue disease involving the skin (eg scleroderma, lupus)
  - Women w/ known or suspected genetic predisposition to breast cancer
  - Others include very young age (<35 yo), multicentric disease, tumor located near nipple, BRCA1 or BRCA2 gene mutation

Lumpectomy

- Selective removal of breast mass & a margin of normal surrounding tissues

Partial or Segmental Mastectomy or Quadrantectomy

- Removal of up to one-quarter of the breast

Mastectomy

- Entire breast removal
  - Women at high risk of breast cancer may be offered prophylactic bilateral mastectomy w/ reconstruction as a risk-reducing surgery

Simple or Total Mastectomy

- Removal of the entire breast, including the nipple, but sparing the axillary LNs or muscle tissue from beneath the breast
- Most common type of mastectomy used to treat breast cancer

Skin-sparing Mastectomy

- Same amount of breast tissue is removed as w/ simple mastectomy but keeping most of the skin over the breast (other than areola & nipple) intact
- Only performed in women who will undergo immediate reconstruction
- May not be suitable for larger tumors or tumors that are close to the skin surface

C SURGERY (CONT'D)

Mastectomy (Cont'd)

Nipple-sparing Mastectomy

- Variation of the skin-sparing mastectomy where breast tissue is removed but sparing the skin & nipple
- Alternative for women who have small early-stage cancer near the outer part of the breast w/ no signs of cancer in the skin or near the nipple

Modified Radical Mastectomy

- Simple mastectomy w/ removal of the axillary LNs
- As effective as radical mastectomy

Radical Mastectomy

- Removal of the entire breast, axillary LNs, & pectoral muscles
- Rarely performed because of disfigurement & side effects
- May still be done for large tumors that are growing into the pectoral muscles under the breast

Lymph Node Surgery

- Includes axillary LN dissection & sentinel LN biopsy
- To assess LN status, ie if the cancer cell has spread to axillary LN
- Important in determining the stage, therapy, & outcome
- Indicated in patients w/ large tumors (eg T2, T3)
- Not usually done in pure DCIS or pure lobular neoplasia

Axillary Lymph Node Dissection

- Removal of 10-40 (usually <20) axillary LNs & examined for cancer metastasis
- Usually performed simultaneously w/ mastectomy or breast-conserving surgery, but may be done in a subsequent operation

Sentinel Lymph Node Biopsy

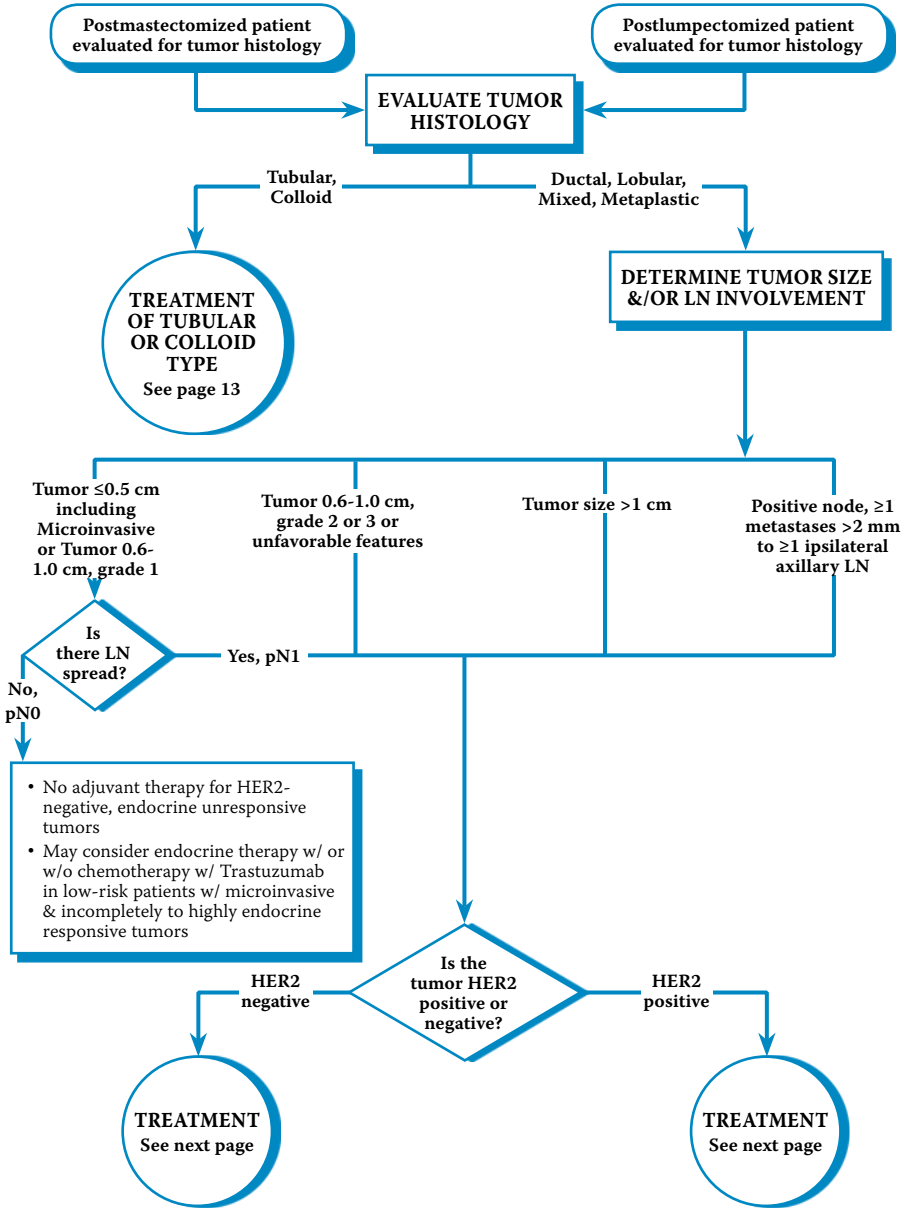
- Removal of the sentinel LN to determine if the cancer cells have spread to nearby LNs
  - The standard of care rather than complete axillary LN excision
  - Sentinel LN is the 1st LN that is most likely to contain cancer cells if metastases have already started
  - Full axillary dissection is done if cancer is found in the sentinel LN
    - Axillary dissection can be safely omitted w/ <2 positive sentinel LNs if whole breast radiation treatment will be given after breast-conserving surgery
  - No further LN surgery is needed if there is no cancer in the sentinel LN
- Decreases the risk of lymphedema because only few LNs are removed
- Considered in patients w/ clinically negative axillary LNs, w/ no previous chemotherapy nor hormone therapy
- Preferred method of axillary LN staging provided that there is an experienced sentinel node team & the patient is an appropriate candidate for sentinel LN biopsy

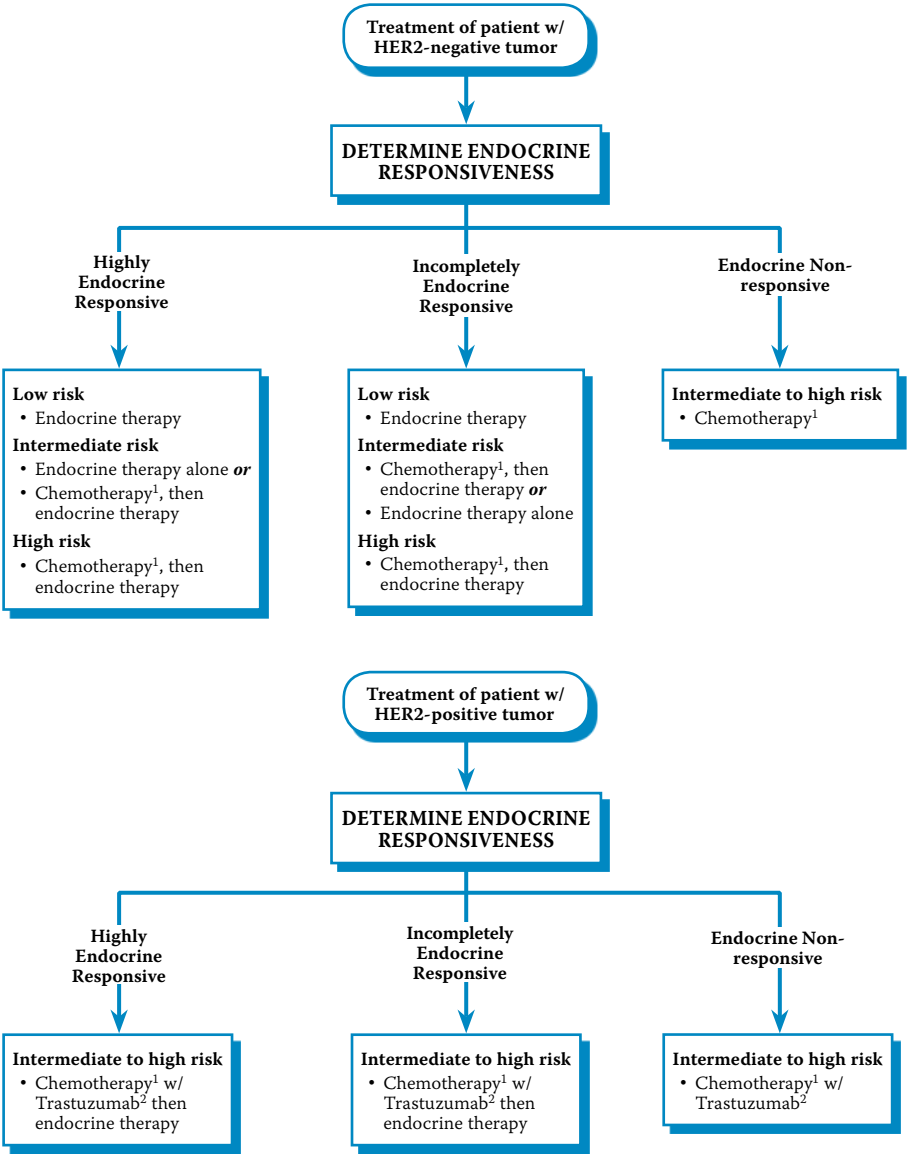
Reconstructive Surgery

- Procedure that restores the breast's appearance
- Offered to patients after mastectomy or breast-conserving surgery which can be done as either immediate breast reconstruction or delayed breast reconstruction

D RADIOTHERAPY

- Treatment w/ high-energy rays or particles that destroy cancer cells
- Radiation to the breast is strongly recommended after breast-conserving surgery to decrease the chance of recurrence
  - Postmastectomy RT is recommended in T3-T4 tumors &/or >4 positive axillary nodes, considered in 1-3 positive axillary nodes & tumors >5 cm or w/ pathologic margins
- Also used to treat cancer that has metastasized to other organs
- Can be given as external beam radiation or brachytherapy
- Commonly done after chemotherapy except in patients w/ negative axillary nodes & tumor w/ ≤5 cm in size & margins ≥1 mm
- RT to the chest wall, supraclavicular & infraclavicular areas, & internal mammary nodes is recommended if w/ positive axillary node involvement
  - RT to the chest wall & internal mammary nodes w/ or w/o radiotherapy to the supraclavicular & infraclavicular nodes can be considered in negative axillary nodes & tumor >5 cm or positive margins
  - RT to the chest only in negative axillary nodes & tumor ≤5 cm w/ close margins of <1 mm


Postmastectomized patient evaluated for tumor histology
Postlumpectomized patient evaluated for tumor histology
EVALUATE TUMOR HISTOLOGY
Tubular, Colloid
Ductal, Lobular, Mixed, Metaplastic
TREATMENT OF TUBULAR OR COLLOID TYPE
See page 13
DETERMINE TUMOR SIZE &/OR LN INVOLVEMENT
Tumor ≤0.5 cm including Microinvasive or Tumor 0.6-1.0 cm, grade 1
Tumor 0.6-1.0 cm, grade 2 or 3 or unfavorable features
Tumor size >1 cm
Positive node, ≥1 metastases >2 mm to ≥1 ipsilateral axillary LN
Is there LN spread?
Yes, pN1
No, pN0
• No adjuvant therapy for HER2-negative, endocrine unresponsive tumors
• May consider endocrine therapy w/ or w/o chemotherapy w/ Trastuzumab in low-risk patients w/ microinvasive & incompletely to highly endocrine responsive tumors
Is the tumor HER2 positive or negative?
HER2 negative
HER2 positive
TREATMENT
See next page
TREATMENT
See next page



[1]For representative chemotherapeutic agents/combinations, please see page 14-
[2]Trastuzumab may be given simultaneously & after chemotherapy or after completion of chemotherapy

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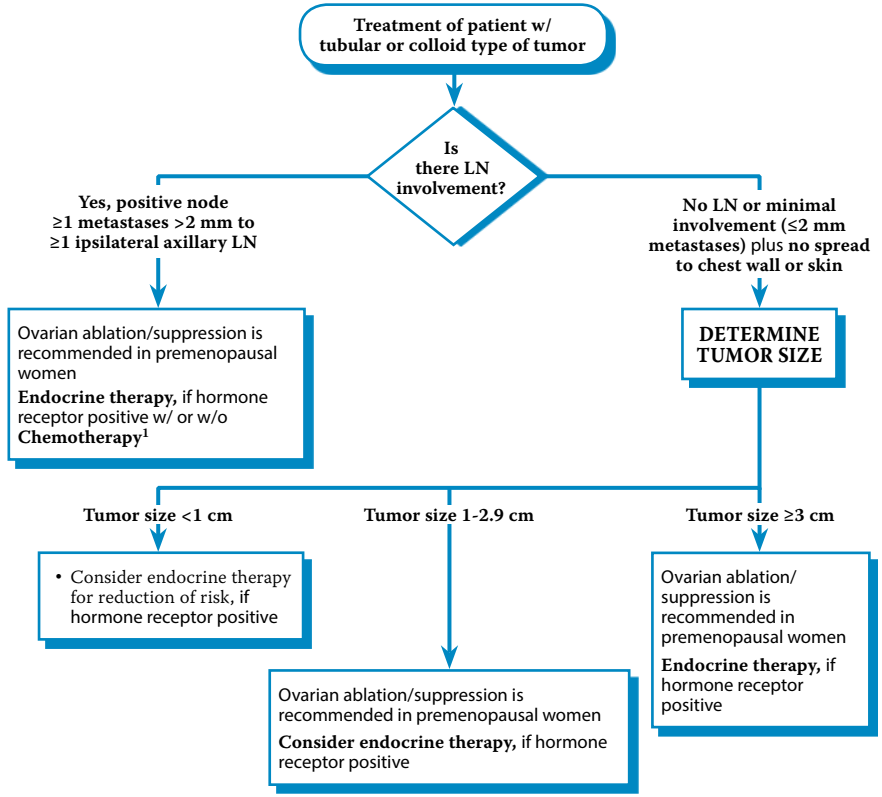

[1]For representative chemotherapeutic agents/combinations, please see page 14

STRATIFICATION FOR SYSTEMIC THERAPY

- Recommended in early breast cancer
- May guide in patient selection for chemotherapy addition
- Patients are further stratified based on responsiveness to endocrine therapy, Trastuzumab & risk for disease recurrence

Categories of Endocrine Responsiveness

Highly Endocrine Responsive
- Majority of tumor cells express high levels of ER & PR

Incompletely Endocrine Responsive
- Lower-level expression of ER &/or PR, or absence of either ER or PR

Endocrine Non-responsive
- Total absence of ER & PR expression

CHEMOTHERAPEUTIC AGENTS FOR EARLY BREAST CANCER

- Several combination treatment regimens are used for adjuvant chemotherapy
  - Usually includes 4-8 cycles of taxane- &/or anthracycline-based regimen
- Chemotherapy response depends on ER status
- Platinum compounds may be given to BRCA1 patients; cells deficient of BRCA1 are hypersensitive to platinum compounds

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CHEMOTHERAPEUTIC AGENTS FOR EARLY BREAST CANCER (CONT'D)

Non-Trastuzumab Combinations (HER2-Negative Disease)

Preferred Adjuvant Regimens:

- Dose-dense Doxorubicin, Cyclophosphamide (AC) followed by Paclitaxel (T) every 2 wks
- Dose-dense Doxorubicin, Cyclophosphamide (AC) followed by Paclitaxel every wk
- Docetaxel, Cyclophosphamide (TC)

Other Adjuvant Regimens:

- Dose-dense Doxorubicin, Cyclophosphamide (AC)
- Doxorubicin, Cyclophosphamide (AC) every 3wk
- Fluorouracil, Doxorubicin, Cyclophosphamide (FAC/CAF)
- Cyclophosphamide, Epirubicin, Fluorouracil (FEC/CEF)
- Cyclophosphamide, Methotrexate, Fluorouracil (CMF)
- Doxorubicin, Cyclophosphamide (AC) followed by Paclitaxel every wk
- Epirubicin, Cyclophosphamide (EC)
- Fluorouracil, Doxorubicin, Cyclophosphamide (FAC) followed by Paclitaxel every wk
- Fluorouracil, Epirubicin, Cyclophosphamide (FEC) followed by Docetaxel
- Fluorouracil, Epirubicin, Cyclophosphamide (FEC) followed by Paclitaxel every wk
- Docetaxel, Doxorubicin, Cyclophosphamide (TAC)
- Doxorubicin, Cyclophosphamide (AC) followed by Docetaxel every 3 wks

Trastuzumab Combinations (HER2-Positive Disease)

Preferred Adjuvant Regimens:

- Doxorubicin, Cyclophosphamide (AC) followed by Paclitaxel (T) plus Trastuzumab w/ or w/o Pertuzumab
- Docetaxel, Carboplatin, Trastuzumab (TCH) w/ or w/o Pertuzumab

Other Adjuvant Regimens:

- Fluorouracil, Epirubicin, Cyclophosphamide (FEC) followed by Docetaxel or Paclitaxel plus Trastuzumab plus Pertuzumab
- Paclitaxel plus Trastuzumab
- Docetaxel plus Cyclophosphamide plus Trastuzumab
- Trastuzumab plus Pertuzumab plus Docetaxel or Paclitaxel followed by Fluorouracil, Epirubicin, Cyclophosphamide (FEC)
- Doxorubicin, Cyclophosphamide (AC) followed by Docetaxel plus Trastuzumab w/ or w/o Pertuzumab

Neoadjuvant only:

- Paclitaxel or Docetaxel plus Trastuzumab plus Pertuzumab then Cyclophosphamide, Epirubicin, Fluorouracil (CEF) plus Trastuzumab

ADJUVANT ENDOCRINE THERAPY

- Offered to patients w/ detectable expression of ER (≥1% invasive cancer cells)
- Minimum duration of therapy is 5 yrs but recent data suggest that extending therapy for an additional 5 yrs reduces risk recurrence & improves disease-free survival
  - Discussion should be made w/ the patient regarding the benefits & risks of extended therapy
- Sequential administration of hormone therapy & chemotherapy is recommended

Aromatase Inhibitors

- Adjuvant treatment in postmenopausal patients w/ ER-positive, stages I & II (tumor size <5 cm) invasive carcinoma
- Based on randomized controlled trials, relative to Tamoxifen, aromatase inhibitors improve clinical outcomes in patients w/ early ER-positive invasive breast cancer; however, treatment was associated w/ increased drug costs & slight decrease in follow-up costs compared to Tamoxifen
- Have the same anti-tumor efficacy & toxicity profiles

Anastrozole

- Recommended for primary adjuvant therapy

Exemestane

- Used as adjuvant therapy following 2-3 yrs of adjuvant Tamoxifen therapy

Letrozole

- Recommended for primary & extended adjuvant therapy following standard Tamoxifen therapy

MONOCLONAL ANTIBODY THERAPY

Trastuzumab

- Indicated for patients who are HER2 positive w/ (nonresponsive, incompletely or highly) endocrine-responsive tumors & low, intermediate or high-risk categories to decrease disease recurrence
  - Indicated for patients w/ early breast cancer who are HER2 positive, given after surgery, adjuvant or neoadjuvant chemotherapy, & radiotherapy (if applicable)
- Can help slow cancer growth & may also stimulate the immune system to more effectively fight the cells
  - Reduces risk of recurrence by half & improves survival
- Given to both premenopausal & postmenopausal patients
- May be given concurrently w/ a taxane following anthracycline or after completion of all chemotherapy
- One yr is the accepted standard treatment duration
- Contraindicated in patients w/ low left ventricular ejection fraction (<50%)

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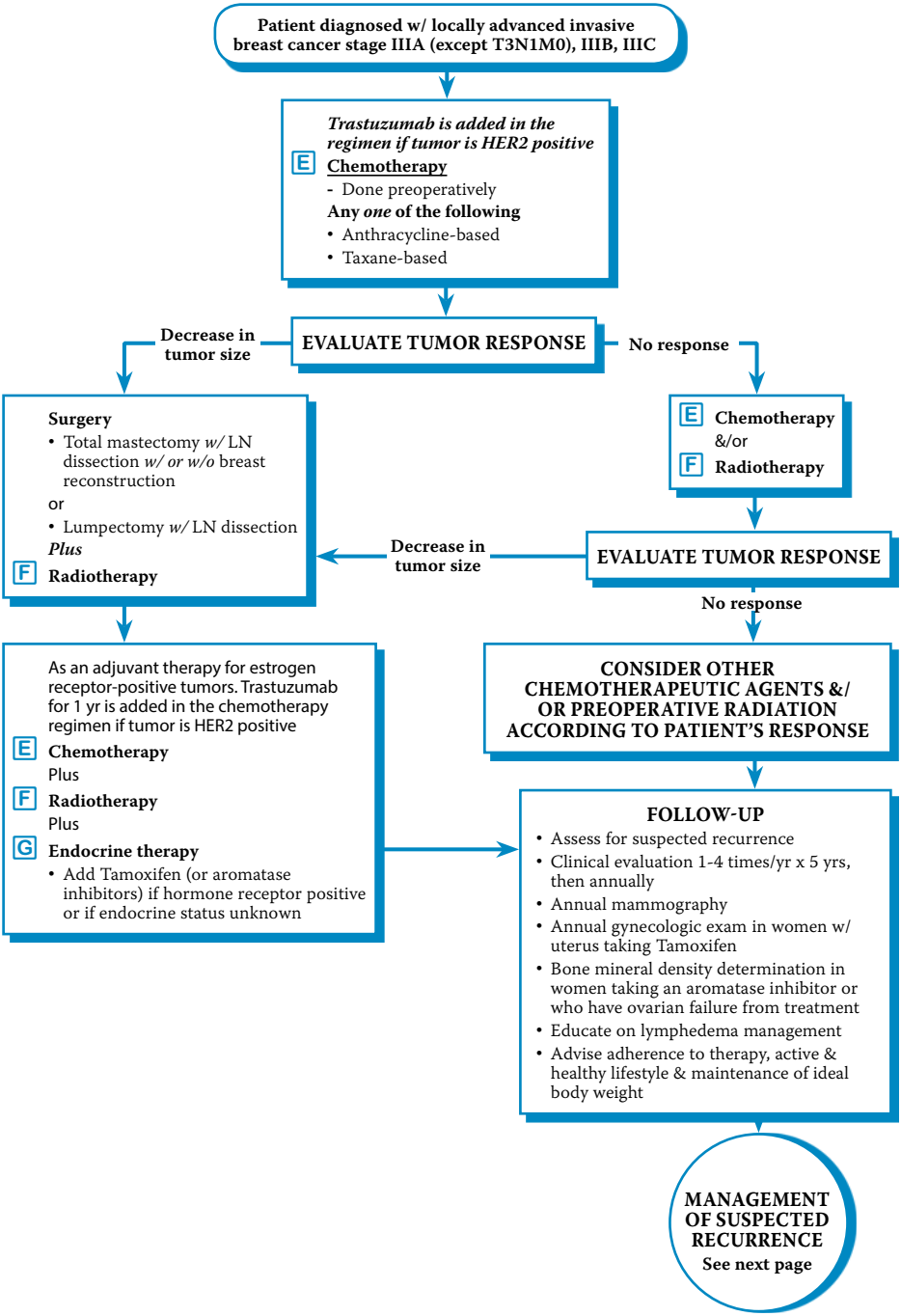
Specific prescribing information may be found in the latest MIMS.



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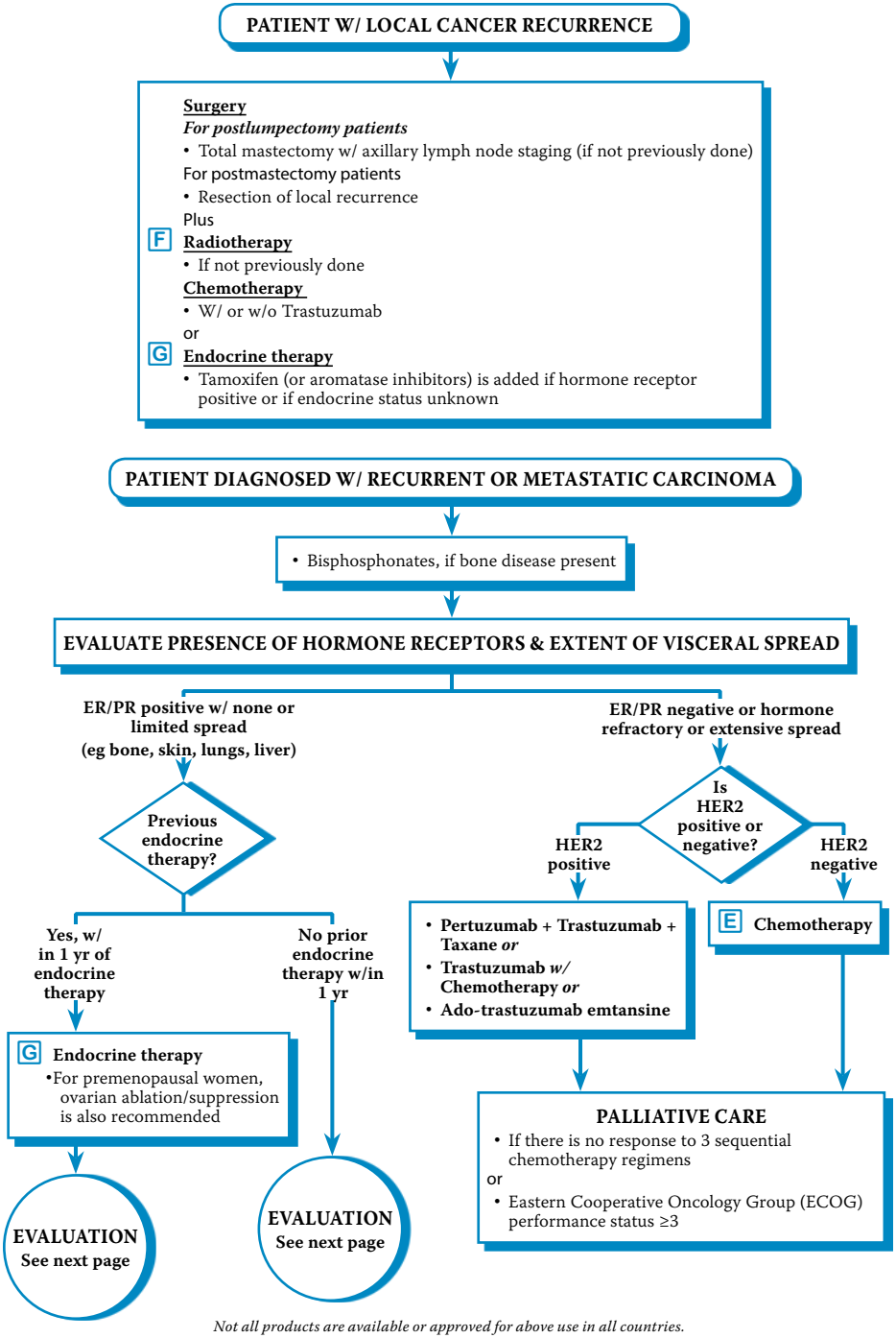

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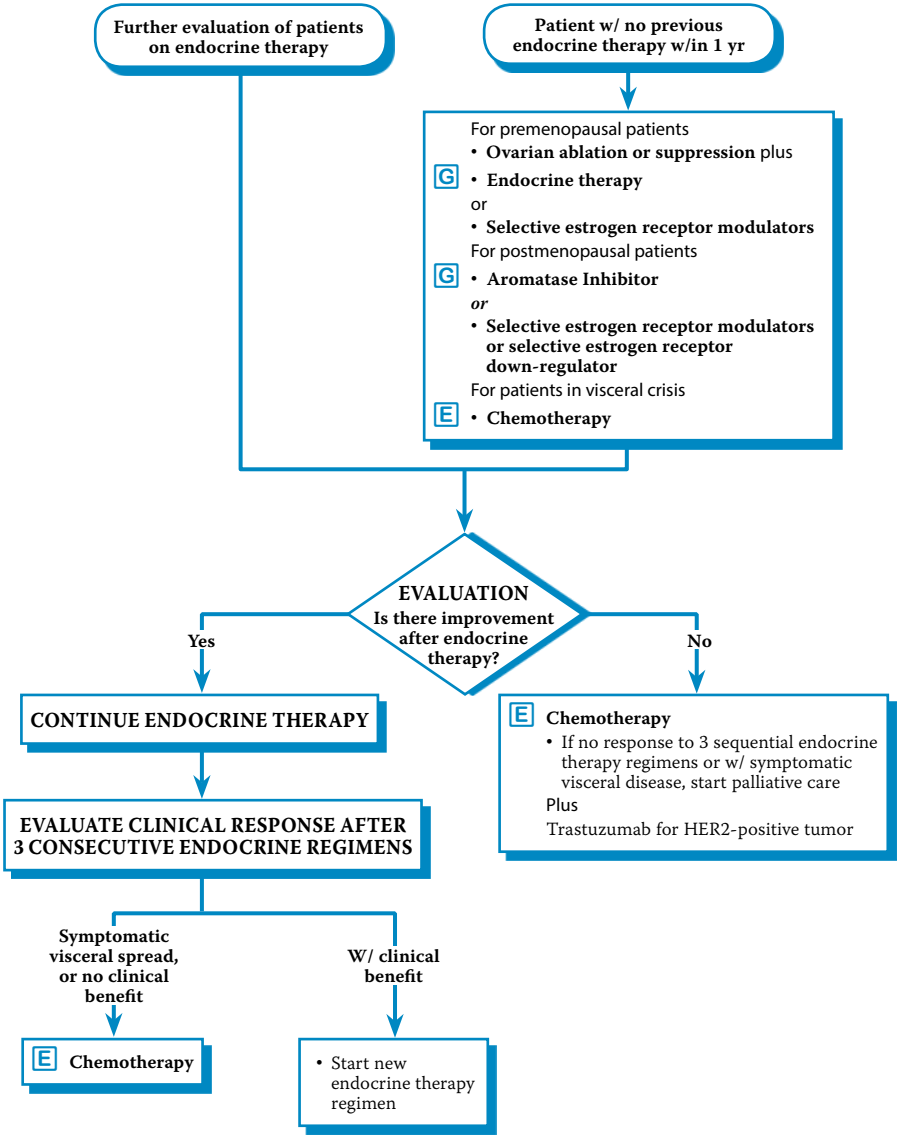

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E CHEMOTHERAPY FOR RECURRENT OR METASTATIC BREAST CANCER

- Consider a taxane- or anthracycline-based regimen
  - Sequential rather than concomitant use is recommended
- Combination of Lapatinib & Capecitabine may be used in patients w/ HER2-positive tumors who are refractory to therapy w/ anthracycline, taxane & Trastuzumab
  - Study has shown that the combination was associated w/ 51% risk reduction of cancer progression
- No evidence states that combination regimens are superior to sequential single agents
- HER2-directed therapy, either as a single agent, combined w/ chemotherapy or w/ endocrine therapy, should be proposed early to patients w/ HER2-positive metastatic breast cancer

Preferred Single Agents:

- Doxorubicin, pegylated liposomal Doxorubicin, Paclitaxel, Capecitabine, Gemcitabine, Vinorelbine & Eribulin

Other Single Agents:

- Cyclophosphamide, Cisplatin, Carboplatin, Docetaxel, albumin-bound Paclitaxel, Epirubicin, Ixabepilone

Combination Regimens:

- Cyclophosphamide, Doxorubicin, Fluorouracil (CAF/FAC)
- Cyclophosphamide, Epirubicin, Fluorouracil (CEF/FEC)
- Doxorubicin, Cyclophosphamide (AC)
- Epirubicin, Cyclophosphamide (EC)
- Cyclophosphamide, Methotrexate, Fluorouracil (CMF)
- Docetaxel & Capecitabine
- Gemcitabine & Paclitaxel (GT)
- Gemcitabine & Carboplatin
- Paclitaxel & Bevacizumab

Preferred 1st-line Agents for HER2-Positive Disease

- Pertuzumab plus Trastuzumab plus Docetaxel
- Pertuzumab plus Trastuzumab plus Paclitaxel

Other Agents for HER2-Positive Disease

- Ado-Trastuzumab emtansine (T-DM1)
- Trastuzumab plus Paclitaxel w/ or w/o Carboplatin
- Trastuzumab plus Docetaxel
- Trastuzumab plus Vinorelbine
- Trastuzumab plus Capecitabine

Agents for Trastuzumab-Exposed HER2-Positive Disease

- Lapatinib plus Capecitabine
- Trastuzumab plus Capecitabine
- Trastuzumab plus Lapatinib (w/o cytotoxic therapy)
- Trastuzumab plus other agents

F RADIOTHERAPY FOR STAGE IIIA (EXCEPT T3N1M0), IIIB, IIIC

- Radiation to the chest wall & supraclavicular nodes is recommended in patients who underwent mastectomy w/ axillary LN surgery & lumpectomy w/ axillary LN dissection
- Internal mammary nodes irradiation is also done if affected

G ENDOCRINE THERAPY

Postmenopausal Patients

Recommended Endocrine Therapy for Stage IV or Recurrent Disease

- Non-steroidal aromatase inhibitors (eg Anastrozole, Letrozole)
- Steroidal aromatase inactivator (eg Exemestane)
- Exemestane plus Everolimus
- Serum estrogen receptor modulators (eg Tamoxifen, Toremifene)
- Estrogen receptor down-regulator (eg Fulvestrant)
- Progestin (eg Megestrol acetate)
- Androgens (eg Fluoxymesterone)
- High-dose estrogen (eg Ethinyl estradiol)
- Palbociclib plus Letrozole
- Palbociclib plus Fulvestrant

Aromatase Inhibitors

- Used in postmenopausal patients
- Preferred 1st-line therapy for recurrent disease in postmenopausal women who have received previous antiestrogen therapy & are w/in 1 yr of antiestrogen exposure
- Used in postmenopausal patients w/ ER- &/or PR-positive, HER2-negative or positive recurrent or stage IV breast cancer w/ no prior endocrine therapy w/in 1 yr

Premenopausal Patients

Endocrine Therapy plus Ovarian Ablation or Suppression or Selective ER Modulators

- Tamoxifen is a standard
- Used in premenopausal patients w/ ER- &/or PR-positive, HER2-negative or positive recurrent or stage IV breast cancer w/ or w/o prior endocrine therapy w/in 1 yr

Other Agents

Bisphosphonates

- Given in addition to endocrine therapy or chemotherapy if bone metastasis is present
- Ibandronic acid, Pamidronate or Zoledronic acid (w/ calcium citrate & vit D)
  - Help strengthen bones & decrease the risk of fractures & bone pains
- Zoledronic acid may be more effective than Pamidronic acid in lytic breast metastasis

Mammalian Target of Rapamycin (mTOR) Pathway Inhibitor

- Inhibits protein in cells that promotes growth & division
- Eg Everolimus
  - Used in addition to Exemestane in postmenopausal women w/ hormone receptor-positive, HER2-negative advanced breast cancer that had progressed or recurred during treatment w/ a nonsteroidal aromatase inhibitor
  - May also stop angiogenesis which can help limit tumor growth

Protein Kinase Inhibitor

- Palbociclib is a highly selective inhibitor of CDK 4/6 kinase activity which is used to treat hormone receptor-positive, HER2-negative advanced or metastatic breast cancer, given w/ Letrozole in postmenopausal women as initial endocrine-based therapy or w/ Fulvestrant in women w/ disease progression after endocrine therapy

MONOCLONAL ANTIBODY THERAPY

Bevacizumab

- May be used to treat metastatic breast cancer which is commonly used in combination w/ Paclitaxel
- Commonly used in combination w/ taxanes (Paclitaxel) & Capecitabine, or also w/ Trastuzumab
- Prevents angiogenesis

Pertuzumab

- A human epidermal growth factor receptor (HER) dimerisation inhibitor preventing HER2 heterodimerisation w/ other HER receptors thereby inhibiting HER signalling pathway activation
- Used in combination w/ Trastuzumab & Docetaxel in the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy
  - Also used for the treatment of locally advanced, inflammatory or early stage HER2-positive breast cancer
- LVEF assessment should be done at baseline & during treatment; discontinue if w/ confirmed clinically significant decline in LV function

Trastuzumab

- Indicated for high-risk, HER2-positive tumor
  - Added in pre-op chemotherapy regimens in patients w/ HER2-positive tumors
- May be used to treat metastatic breast cancer, w/ or w/o chemotherapy
  - May be given as monotherapy to patients w/ HER2-overexpressing tumors who have received at least 2 regimens of chemotherapy for metastatic disease
- May be used as adjuvant therapy along w/ chemotherapy in cancer recurrence risk reduction & as neoadjuvant therapy w/ chemotherapy to reduce the tumor size prior to surgical operation
- Combination w/ an anthracycline is related to significant cardiac toxicity, except as part of the neoadjuvant Trastuzumab w/ Paclitaxel followed by CEF regimen

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Dosage Guidelines

AGENT AFFECTING BONE METABOLISM

Drug	Dosage	Remarks
Raloxifene	**Risk reduction for invasive breast cancer in postmenopausal women:** 60 mg PO 24 hrly	**Adverse Reactions** • Hot flushes, leg cramps, peripheral edema, endometrial fluid accumulation, thromboembolic events [deep venous thrombosis (DVT), pulmonary embolism] • Rare: Headache, rashes, hypertension, mild breast symptoms, GI disturbance, thrombocytopenia **Special Instructions** • Use w/ caution in women w/ risk factors for stroke & venous thromboembolism, in moderate renal impairment • Contraindicated in women w/ history of thromboembolic disorders, hepatic & severe renal impairment

ANABOLIC AGENT

Drug	Dosage	Remarks
Nandrolone	25-50 mg IM every 3 wk	**Adverse Reactions** • Virilization in women, suppression of ovarian activity, atrophy of breasts & endometrial tissue, amenorrhea; Other effects (water & salt retention, edema, increased vascularity of the skin & bone growth) **Special Instructions** • Use w/ caution in patients w/ renal or hepatic dysfunction, hypertension, epilepsy, migraine; diabetic patients may need dose adjustments of antidiabetic drugs • Avoid in patients w/ nephrosis or nephrotic phase of nephritis, cardiac & renal failure, liver disease w/ impaired bilirubin excretion, hepatic carcinoma, edema

ANDROGENS & RELATED SYNTHETIC DRUGS

Drug	Dosage	Remarks
Testosterone enanthate	200-400 mg IM every 2-4 wk	**Adverse Reactions** • Amenorrhea, menstrual irregularities, inhibition of gonadotropin secretion, virilization; Other effects (water retention, nausea, headache, changes in libido, acne, alterations in LFTs) **Special Instructions** • Observe for signs of virilization • Use w/ caution in patients w/ history of severe heart, liver & kidney disease • Avoid in patients who are or may become pregnant

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Dosage Guidelines

CANCER HORMONE THERAPY		
Drug	**Dosage**	**Remarks**
Antiestrogen Agents[1]		
Fulvestrant	250 mg slow IM inj, 1 in each buttock, at 1 mth intervals w/ additional 500 mg after 2 wk	**Adverse Reactions** • Local inj site reactions, asthenia, nausea, elevated hepatic enzymes **Special Instructions** • Use w/ caution in patients w/ mild to moderate hepatic impairment, severe renal impairment, bleeding diatheses, thrombocytopenia, on anticoagulants, potential risk of osteoporosis; thrombolic events in patients w/ advanced breast cancer • Avoid in patients w/ severe hepatic impairment
Tamoxifen	20 mg/day PO in single or divided doses (morning & evening). If no response w/in 1 mth, may increase dosage to 40 mg/day in single or divided doses	**Adverse Reactions** • CV effects (edema, chest pain, flushing, hypertension); GI effects (nausea, wt loss, diarrhea, abdominal pain); CNS effects (fatigue, pain, dizziness, insomnia, depression); Dermatologic effects (rash, alopecia); Other effects (menstrual disorder, hot flushes, weakness, vag discharge, leukopenia, thrombocytopenia, hypercholesterolemia) **Special Instructions** • Use w/ caution in patients w/ history of deep vein thrombosis or pulmonary embolism • Associated w/ increased risk of uterine or endometrial cancer
Enzyme Inhibitors		
Anastrozole	1 mg PO daily Same dose for elderly patients **Duration of treatment when used as adjuvant:** 5 yrs	**Adverse Reactions** • GI effects (N/V, changes in wt, abdominal pain, bowel movement changes); CNS effects (fatigue, headache, dizziness, depression); CV effects (hypertension, edema); Dermatologic effects (alopecia, rash, pruritus); Other effects (cough, dyspnea, infection, decreased bone mineral density, weakness, hot flashes, hypercholesterolemia) **Special Instructions** • Take doses w/ breakfast & dinner • If medication is missed for ≥3 days, restart at lowest dose & increase to current dose • Maintain adequate hydration • Treatment should be maintained at maximum tolerated dose • Avoid in patients w/ severe renal or hepatic impairment • Use w/ caution in patients w/ supraventricular cardiac conduction abnormalities, patients w/ seizures, COPD, asthma, risk of GI bleeding or in patients w/ bladder outlet obstruction, mild-moderate liver or renal dysfunction • No dosage adjustment is needed in the elderly
Exemestane	25 mg PO daily Complete the duration of 5 yrs combined w/ simultaneous adjuvant hormonal therapy or earlier if tumor relapse appears in early breast cancer or until progression of tumor is evident esp in advanced breast cancer	
Letrozole	2.5 mg PO daily Same dose for elderly patients	

[1] Various antiestrogens are available. Specific prescribing information may be found in the latest MIMS.

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Dosage Guidelines

CANCER HORMONE THERAPY (CONT'D)		
Drug	**Dosage**	**Remarks**
Gonadotropin-Releasing Hormone Analogs		
Goserelin	3.6 mg depot SC inj into anterior abdominal wall every 28 days	**Adverse Reactions** • Hypoestrogenism (transient vag bleeding, hot flushes, vag dryness, decreased libido, breast tenderness, insomnia, depression, irritability & fatigue, decreased elasticity of the skin, headache, osteoporosis after several wk of treatment); GI effects (nausea, abdominal discomfort); Other effects (transient increase in menstrual bleeding, reduction in glucose tolerance can develop, changes in serum lipids & hepatic effects, hypersensitivity reactions) **Special Instructions** • Avoid in patients w/ hypersensitivity to Goserelin, Leuprorelin, or other GnRH analogs • Use w/ caution in patients w/ metabolic bone disease, polycystic ovarian syndrome, patients at risk of ureteric obstruction or spinal cord compression; may cause uterine cervical resistance, risk of developing ovarian hyperstimulation syndrome
Leuprorelin	3.75 mg SC/IM inj once every 28 days	
Progestogens		
Medroxy-progesterone acetate	400-1500 mg/day PO or 500-1000 mg/day IM x 28 days then 500 mg IM twice wkly	**Adverse Reactions** • CNS effects (loss of concentration, nervousness, insomnia, somnolence, fatigue, dizziness, depression, vision disorders, headache); Other effects (breast tenderness, abnormal uterine bleeding, amenorrhea, prolonged anovulation, GI & hepatobiliary disorders, WBC & platelet count elevation) **Special Instructions** • Use w/ caution in patients w/ cushingoid symptoms, suppressed adrenal function, diabetes &/or arterial HTN, epilepsy, asthma, cardiac & renal dysfunction, history of mental depression • Discontinue if w/ papilloedema or retinal vascular lesion, jaundice or liver function deterioration, significant increase in BP, new onset of migraine-type headache • Avoid in patients w/ thrombophlebitis, thromboembolic disorders, hypercalcemia w/ osseous metastases, impaired liver function or active liver disease, missed abortion, metrorrhagia, undiagnosed vag bleeding, suspected & early breast carcinoma
Megestrol acetate	160 mg PO 24 hrly x 2 mth	**Adverse Reactions** • Wt gain; occasionally N/V, edema, breakthrough uterine bleeding **Special Instructions** • Use w/ caution in patients w/ history of severe liver impairment, thrombophlebitis, galactose intolerance, glucose-galactose malabsorption, Lapp lactase deficiency • Avoid in patients w/ hypersensitivity

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Dosage Guidelines

ADJUVANT COMBINATION THERAPY REGIMENS FOR BREAST CANCER

COMBINATION THERAPY REGIMENS

Drug	Dosage	Remarks
5-Fluorouracil + Doxorubicin + Cyclophosphamide	**5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 or days 1 & 4 **Doxorubicin:** 50 mg/m^2 IV on day 1 (or by 72 hrs continuous IV infusion) **Cyclophosphamide:** 500 mg/m^2 IV on day 1 Cycled every 21 days for 6 cycles	**Adverse Reactions** **Cyclophosphamide** • GI effects (N/V, anorexia, mucositis); CNS effect (headache); GU effect (acute hemorrhagic cystitis or urinary fibrosis); Dermatologic effects (alopecia, rash); Hematologic effect (leukopenia); Resp effects (rhinorrhea, nasal congestion); Other effects (fertility impairment, renal tubular necrosis, SIADH may occur w/ doses >50 mg/kg) **Docetaxel** • Ophtha effect (epiphora w/ canalicular stenosis); CNS effects (paresthesia, dysesthesia, pain); Dermatologic effects (alopecia, rash, erythema, desquamation, anaphylaxis); GI effects (N/V, stomatitis, diarrhea); CV effects (hypotension, edema); Hematologic effects (neutropenia, leukopenia, anemia, thrombocytopenia); Other effects (weakness, bronchospasm, increased transaminases) **Doxorubicin** • Dermatologic effects (inj site reaction, alopecia, urticaria, rash); GI effects (N/V, stomatitis, GI ulceration, diarrhea, loss of appetite); GU effects (urinary frequency, hematuria); Hematologic effects (leukopenia, anemia, thrombocytopenia); CV effects (transient ECG abnormalities, CHF); Other effects (discoloration of body fluids, hyperuricemia, infertility) **Epirubicin** • CNS effects (changes in sensorium, fever); Dermatologic effects (inj site reaction, alopecia, anaphylaxis, rash); GI effects (N/V, diarrhea, loss of appetite); Hematologic effects (leukopenia, anemia, thrombocytopenia); Other effects (menstrual dysfunction, hot flushes) **Fluorouracil** • CV effects (myocardial ischemia, angina); CNS effects (confusion, headache, acute cerebellar syndrome); Dermatologic effects (alopecia, rash, vein pigmentation, palmar-plantar erythrodysesthesia syndrome, anaphylaxis); GI effects (bleeding, esophagopharyngitis, N/V, ulceration); Hematologic effects (leukopenia, anemia, thrombocytopenia); Ophtha effects (photophobia, visual disturbances, lacrimation, nystagmus); Other effect (nose bleeding)
5-Fluorouracil + Doxorubicin + Cyclophosphamide + Paclitaxel	**5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 or days 1 & 4 **Doxorubicin:** 50 mg/m^2 IV on day 1 (or by 72 hrs continuous IV infusion) **Cyclophosphamide:** 500 mg/m^2 IV on day 1 Cycled every 21 days for 6 cycles ***Followed by:*** **Paclitaxel:** 80 mg/m^2 IV infusion for 1 hr wkly x 12 wks	
Cyclophosphamide + Doxorubicin + 5-Fluorouracil	**Cyclophosphamide:** 100 mg/m^2 PO on days 1-14 **Doxorubicin:** 30 mg/m^2 IV on days 1 & 8 **5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 Cycled every 28 days for 6 cycles	
Docetaxel + Doxorubicin + Cyclophosphamide	**Docetaxel:** 75 mg/m^2 IV on day 1 **Doxorubicin:** 50 mg/m^2 IV on day 1 **Cyclophosphamide:** 500 mg/m^2 IV on day 1 Cycled every 21 days for 6 cycles*	
Doxorubicin + Cyclophosphamide	**Doxorubicin:** 60 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 Cycled every 14 days for 4 cycles	
Docetaxel + Cyclophosphamide	**Docetaxel:** 75 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 Cycled every 21 days for 4 cycles	

*All cycles are w/ Filgrastim support. Specific prescribing information on Filgrastim may be found in the latest MIMS.

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Dosage Guidelines

ADJUVANT COMBINATION THERAPY REGIMENS FOR BREAST CANCER

COMBINATION THERAPY REGIMENS (CONT'D)

Drug	Dosage	Remarks
Epirubicin + Cyclophosphamide	**Epirubicin:** 100 mg/m^2 IV on day 1 **Cyclophosphamide:** 830 mg/m^2 IV on day 1 Cycled every 21 days for 8 cycles	**Adverse Reactions (Cont'd)** Methotrexate • GI effects (stomatitis, gingivitis, N/V, diarrhea, loss of appetite, intestinal perforation); CNS effect (dizziness); Dermatologic effects (alopecia, rash, severe reactions eg Stevens-Johnson syndrome, toxic epidermal necrolysis); Hematologic effects (leukopenia, thrombocytopenia); Other effects (hyperuricemia, menstrual dysfunction, fever, chills) **Paclitaxel (Albumin bound)** • CV effects (ECG abnormality, edema, hypotension); GI effects (N/V); Hematologic effects (neutropenia, anemia); Hepatic effect (elevated liver enzymes); Other effects (candidiasis infection, vision disturbances, sensory neuropathy) **Paclitaxel (Conventional)** • Dermatologic effects (rash, alopecia, inj site reaction, hypersensitivity reaction); CV effects (edema, flushing, bradycardia); GI effects (N/V, stomatitis, mucositis, diarrhea); Hematologic effects (neutropenia, leukopenia); Hepatic effect (elevated liver enzymes); Other effect (peripheral neuropathy) **Trastuzumab** • CNS effects (headache, dizziness, insomnia, peripheral neuritis); Dermatologic effects (acne, rash, severe hypersensitivity reaction eg anaphylaxis); GI effects (abdominal pain, anorexia, N/V, diarrhea); CV effects (edema, palpitation, hypotension, heart failure); Hematologic effects (leukopenia, anemia); Other effects [infusion related symptoms (eg fever, chills); rash, weakness, back pain, dyspnea, cough] **Special Instructions** **Cyclophosphamide** • Use w/ caution in patients w/ hepatic or renal impairment **Docetaxel** • Contraindicated in patients w/ preexisting bone marrow suppression w/ neutrophil count of <1500 cells/mm^3, & patients w/ hepatic impairment **Doxorubicin** • Avoid in patients w/ preexisting bone marrow suppression & CHF • Use w/ caution in patients w/ previous radiation therapy • Baseline cardiac evaluation (ECG, LVEF) is advised esp in patients at high risk of cardiac toxicity • May cause secondary leukemia
Cyclophosphamide + Methotrexate + 5-Fluorouracil	**Cyclophosphamide:** 100 mg/m^2 PO on days 1-14 **Methotrexate:** 40 mg/m^2 IV on days 1 & 8 **5-Fluorouracil:** 600 mg/m^2 IV on days 1 & 8 Cycled every 28 days for 6 cycles	
Dose-dense Doxorubicin + Cyclophosphamide + Paclitaxel	**Doxorubicin:** 60 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 *Cycled every 14 days for 4 cycles*[*] ***Followed by:*** **Paclitaxel:** 175 mg/m^2 IV infusion over 3 hr on day 1 Cycled every 14 days for 4 cycles*	

[*]All cycles are w/ Filgrastim support. Specific prescribing information on Filgrastim may be found in the latest MIMS.

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Dosage Guidelines

ADJUVANT COMBINATION THERAPY REGIMENS FOR BREAST CANCER

COMBINATION THERAPY REGIMENS (CONT'D)

Drug	Dosage	Remarks
Dose-dense Doxorubicin + Cyclophosphamide + Paclitaxel	**Doxorubicin:** 60 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 *Cycled every 14 days for 4 cycles** ***Followed by:*** **Paclitaxel:** 80 mg/m^2 IV infusion for 1 hr wkly x 12 wks	**Special Instructions (Cont'd)** **Epirubicin** • Avoid in patients w/ cardiac disease (severe myocardial insufficiency, severe arrhythmias & recent MI) & in patients w/ baseline neutrophil count 1500 cells/mm^3 • Use w/ caution in patients w/ preexisting cardiac disease, hepatic & renal dysfunction & in patients who have previously received anthracyclines • May cause secondary leukemia **Fluorouracil** • Contraindicated in patients w/ dihydropyrimidine dehydrogenase (DPD) enzyme deficiency • Use w/ caution in patients w/ hepatic or renal impairment, patients w/ high-dose pelvic radiation or previous exposure to alkylating agents **Methotrexate** • Use w/ caution in patients w/ preexisting bone marrow suppression, renal or hepatic impairment, peptic ulcer disease & ulcerative colitis **Paclitaxel (Albumin bound)** • Contraindicated in patients w/ baseline neutrophil count of <1500 cells/mm^3 • Use w/ caution in patients w/ renal or hepatic dysfunction **Paclitaxel (Conventional)** • Use w/ caution in patients w/ hepatic dysfunction **Trastuzumab** • Use w/ caution in patients w/ preexisting cardiac disease, previous exposure to radiation therapy or anthracyclines • Monitor cardiac function at baseline, during & after treatment
5-Fluorouracil + Epirubicin + Cyclophosphamide + Docetaxel	**5-Fluorouracil:** 500 mg/m^2 IV on day 1 **Epirubicin:** 100 mg/m^2 IV on day 1 **Cyclophosphamide:** 500 mg/m^2 IV on day 1 *Cycled every 21 days for 3 cycles* ***Followed by:*** **Docetaxel:** 100 mg/m^2 IV on day 1 *Cycled every 21 days for 3 cycles*	
Doxorubicin + Cyclophosphamide + Paclitaxel + Trastuzumab	**Doxorubicin:** 60 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 *Cycled every 21 days for 4 cycles* ***Followed by:*** **Paclitaxel:** 80 mg/m^2 IV infusion over 1 hr wkly for 12 wk **w/** **Trastuzumab:** 4 mg/kg IV w/ 1st dose of Paclitaxel ***Followed by:*** **Trastuzumab:** 2 mg/kg IV wkly to complete 1 yr ***Alternative:*** Trastuzumab 6 mg/kg IV every 3 wks following completion of Paclitaxel, & given to complete 1 yr of Trastuzumab treatment	

*All cycles are w/ Filgrastim support. Specific prescribing information on Filgrastim may be found in the latest MIMS.

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Dosage Guidelines

NEOADJUVANT COMBINATION THERAPY REGIMENS FOR BREAST CANCER

COMBINATION THERAPY REGIMENS

Drug	Dosage	Remarks
Trastuzumab + Pertuzumab + Docetaxel or Paclitaxel + 5-Fluorouracil + Epirubicin + Cyclophosphamide	**Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV **Pertuzumab:** 840 mg IV on day 1 followed by 420 mg IV **Docetaxel:** 75-100 mg/m^2 IV on day 1 ***or*** **Paclitaxel:** 80 mg/m^2 IV on days 1, 8, 15 Cycled every 21 days for 4 cycles ***Followed by:*** **5-Fluorouracil:** 600 mg/m^2 IV on day 1 **Epirubicin:** 90 mg/m2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 Cycled every 21 days for 3 cycles ***Followed by:*** **Trastuzumab:** 6 mg/kg IV every 21 days to complete 1 yr of Trastuzumab treatment	**Adverse Reactions** **Cyclophosphamide** • See Cyclophosphamide on page 23 **Docetaxel** • See Docetaxel on page 23 **Epirubicin** • See Epirubicin on page 23 **Fluorouracil** • See Fluorouracil on page 23 **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 24 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 24 **Pertuzumab** • GI effects (diarrhea, decreased appetite, mucositis, N/V, stomatitis); Dermatologic effects (rash, pruritus); Hematologic effects (neutropenia, anemia); Others (fatigue, headache, fever, upper respiratory tract infection) • Effects w/ combination therapy: Heart failure, dyspnea, decreased left ventricular ejection fraction (LVEF), pleural effusion, sepsis **Trastuzumab** • See Trastuzumab on page 24 **Special Instructions** **Cyclophosphamide** • See Cyclophosphamide on page 24 **Docetaxel** • See Docetaxel on page 24 **Epirubicin** • See Epirubicin on page 25 **Fluorouracil** • See Fluorouracil on page 25 **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 25 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 25 **Pertuzumab** • Assess LVEF at baseline & during therapy because of risk of heart failure • Contraindicated in patients w/ hypersensitivity to Pertuzumab **Trastuzumab** • See Trastuzumab on page 25

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Dosage Guidelines

MONOTHERAPY AGENTS FOR RECURRENT OR METASTATIC BREAST CANCER

CYTOTOXIC CHEMOTHERAPY

Drug	Dosage	Remarks
Capecitabine	1000-1250 mg/m^2 PO 12 hrly x 14 days Cycled every 21 days	**Adverse Reactions** **Capecitabine** • GI effects (diarrhea, N/V, abdominal pain, stomatitis, constipation, dyspepsia, flatulence); Hematologic effects (neutropenia, anemia, lymphopenia); CNS effects (anorexia, insomnia, depression, headache, dizziness); Pulmonary effects (nasopharyngitis, lower respiratory tract infection, rhinorrhea, cough, dyspnea); CV effect (edema); Other effects (fatigue, hand-foot syndrome, increased blood bilirubin) **Chlorambucil** • GI effects (N/V, diarrhea, hepatotoxicity); acute secondary hematologic malignancies; Rarely irreversible bone marrow failure, allergic reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, seizures, peripheral neuropathy, interstitial pulmonary fibrosis or pneumonia **Cyclophosphamide** • See Cyclophosphamide on page 23 **Docetaxel** • See Docetaxel on page 23 **Doxorubicin** • See Doxorubicin on page 23 **Epirubicin** • See Epirubicin on page 23 **Gemcitabine** • CV effect (edema); CNS effects (pain, fever); GI effects (diarrhea, paralytic ileus, N/V); Dermatologic effects (rash, alopecia, pruritus); Hepatic effects (elevated liver enzymes & total bilirubin level); Other effects (bone marrow suppression, hemolytic uremic syndrome) **Idarubicin** • GI effects (N/V, diarrhea, abdominal pain, GIT bleeding, elevation of liver enzymes & bilirubin); CV effects (bradycardia, sinus tachycardia, tachyarrhythmia, asymptomatic reduction of left ventricular ejection fraction, CHF, local phlebitis, thrombophlebitis); Other effects (decreased blood cell counts, red coloration of urine 1-2 days after treatment, rash, itch, fever) **Ifosfamide** • GI effects (N/V); Other effects (myelosuppression, hemorrhagic cystitis, renal tubular & glomerular dysfunction, encephalopathy, alopecia) **Ixabepilone** • GI effects (N/V, diarrhea, stomatitis, mucositis); Hematologic effects (neutropenia, leukopenia, thrombocytopenia); Other effects (peripheral sensory neuropathy, myalgia, arthralgia, fatigue, asthenia, alopecia, musculoskeletal pain) **Melphalan** • Dermatologic effects (rashes, hypersensitivity, skin ulceration, necrosis, alopecia); GI disturbances, pulmonary fibrosis, hemolytic anemia, bone marrow depression, myalgia, flu-like symptoms **Mitomycin-C** • GI effects (N/V), gastritis, diarrhea); Hematologic effects (thrombocytopenia, leukopenia, anemia); Other effects (renal failure, hypertension, edema, hematuria, hemolytic-uremic syndrome, marrow depression, interstitial pneumonia)
Chlorambucil	0.2 mg/kg/day PO x 6 wk	
Cyclophos-phamide	50 mg PO 24 hrly on days 1-21 Cycled every 28 days	
Docetaxel	60-100 mg/m^2 IV infusion over 1 hr *Cycled every 21 days* ***or*** 35 mg/m^2 IV infusion over 1 hr wkly x 6 wk followed by 2 wks rest period, then repeat Premedication w/ corticosteroids, Diphenhydramine & H2-antagonist is required for all patients	
Doxorubicin	60-75 mg/m^2 BSA IV every 21 days or 20 mg/m^2 IV wkly	
Doxorubicin (Pegylated liposomal)	50 mg/m^2 BSA IV infusion over 60 mins every 4 wks as long as patients do not progress & continue to tolerate treatment Initial dose administered at ≤1 mg/min to minimize infusion reactions 250 mL dextrose 5% in water dilution for <90 mg 500 mL dextrose 5% in water dilution for ≥90 mg Cycled every 28 days	

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Dosage Guidelines

MONOTHERAPY AGENTS FOR RECURRENT OR METASTATIC BREAST CANCER

CYTOTOXIC CHEMOTHERAPY (CONT'D)

Drug	Dosage	Remarks
Epirubicin	60-90 mg/m^2 IV on day 1 Cycled every 21 days as monotherapy	**Adverse Reactions (Cont'd)** **Mitoxantrone** • GI effects (N/V, diarrhea, abdominal pain, anorexia, constipation); CV effects (asymptomatic decrease in left ventricular ejection fraction, transient ECG changes, arrhythmia); CNS effects (somnolence, neuritis, confusion, cramps, anxiety, paresthesia): Other effects (transient leukopenia, thrombocytopenia, anemia; bluish discoloration of sclerae, urine, or skin & nails) **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 24 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 24 **Tegafur** • GI effects (N/V, anorexia, diarrhea); Other effects (thrombocytopenia, malaise, pigmentation) **Vinblastine** • Dermatologic effects (skin reactions, alopecia): Other effects (leukopenia, GI upset, neurological effects, ischemic cardiotoxicity, SIADH) **Vincristine** • Dermatologic effect (alopecia); CV effects (orthostatic hypotension or hypertension); CNS effects (depression, headache, insomnia, fever); GI effects (anorexia, bloating, paralytic ileus) **Vinorelbine** • CNS effect (fatigue); GI effects (constipation, paralytic ileus, N/V); Hematologic effects (bone marrow suppression, severe granulocytopenia, leukopenia); Hepatic effects (elevated AST & total bilirubin level); Other effects (alopecia, inj site reaction, weakness) **Special Instructions** **Capecitabine** • Contraindicated in patients w/ severe renal/hepatic impairment, dihydropyrimidine dehydrogenase deficiency, severe leukopenia, neutropenia or thrombocytopenia • Use w/ caution in patients w/ renal impairment, mild-mod hepatic dysfunction, galactose intolerance, patients taking oral coumarin-derivative anticoagulants • Monitor ALT, AST, serum electrolytes **Chlorambucil** • Avoid in 1st trimester pregnancy • Use w/ caution in patients w/ renal or hepatic impairment, seizure disorder, patients immunized w/ live vaccine • Monitor blood counts closely **Cyclophosphamide** • See Cyclophosphamide on page 24 **Docetaxel** • See Docetaxel on page 24 **Doxorubicin** • See Doxorubicin on page 24
Eribulin	1.4 mg/m^2 IV on days 1 & 8 Cycled every 21 days	
Gemcitabine	800-1200 mg/m^2 IV infusion over 30 min on days 1, 8 & 15 Cycled every 28 days	
Idarubicin	45 mg/m^2 PO 24 hrly or 15 mg/m^2 PO 24 hrly x 3 days To be repeated every 3-4 wk based on hematological recovery	
Ifosfamide	**Fractionated administration:** 50-60 mg/kg/day IV x 5 days (total dose/cycle: 250-300 mg/kg) at 3-4 wk intervals or 125-200 mg/kg/day single IV infusion	
Ixabepilone	40 mg/m^2 IV on day 1 Cycled every 21 days	
Melphalan	0.15 mg/kg body wt or 6 mg/m^2 BSA/day PO for 5 days & repeated every 6 wk	
Mitomycin	**Intermittent administration:** 4-6 mg IV 24 hrly 1-2 times wkly **Continuous administration:** 2 mg IV 24 hrly **Large dose intermittent administration:** 10-30 mg IV 24 hrly at 1-3 wk intervals	

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Dosage Guidelines

MONOTHERAPY AGENTS FOR RECURRENT OR METASTATIC BREAST CANCER

CYTOTOXIC CHEMOTHERAPY (CONT'D)

Drug	Dosage	Remarks
Mitoxantrone	14 mg/m^2 single IV dose May be repeated after 21 days	**<u>Special Instructions</u> (Cont'd)** **Epirubicin** • See Epirubicin on page 25 **Gemcitabine** • Use w/ caution in patients w/ hepatic metastasis, hepatic or renal impairment, w/ concurrent radiation therapy **Idarubicin** • Use w/ caution in patients w/ secondary leukemia, galactose intolerance, Lapp-lactase deficiency, glucose-galactose malabsorption; increased susceptibility to infections • Monitor hematologic profiles, cardiac, hepatic & renal function prior & during treatment • Avoid in patients w/ uncontrolled infection, persistent myelosuppression, severe renal & hepatic impairment, severe myocardial insufficiency, recent MI, severe arrhythmias **Ifosfamide** • Use w/ caution in patients w/ previous radiotherapy, chronic hepatic & renal impairment, diabetes mellitus, brain metastases, cerebral symptoms, deteriorated renal function; always administer w/ uroprotective agent Mesna • Avoid in patients w/ severely impaired bone marrow function, florid infections, impaired kidney function &/or urinary tract obstruction, cystitis **Ixabepilone** • Use w/ caution in patients w/ diabetes mellitus, history of cardiac disease, AST or ALT >5 or bilirubin >3 x upper limit of normal • Monitor peripheral blood counts & for neuropathy symptoms • Contraindicated in patients w/ history of severe hypersensitivity to agents containing Cremophor EL or its derivatives, neutrophils <1500 cells/mm^3 or platelet count <100,000 cells/mm^3 **Melphalan** • Use w/ caution in pregnancy, in patients w/ renal impairment, & in those who have just received radiotherapy or cytotoxic agents • Monitor blood counts • Contraindicated in lactating women **Mitomycin-C** • Observe for evident renal toxicity • Monitor patient frequently w/ lab tests, infectious disease, bleeding tendency • Avoid in patients w/ thrombocytopenia, coagulation disorder, or increased bleeding tendencies, hepatic failure, renal impairment & bone marrow suppression **Mitoxantrone** • Use w/ caution in patients w/ history of anthracycline therapy, changes in cardiac function, severe hepatic insufficiency • Monitor blood count during treatment • Avoid in patients w/ severe bone marrow suppression
Paclitaxel (Albumin-bound)	260 mg/m^2 IV infusion over 30 mins *Cycled every 21 days* ***or*** 100 or 150 mg/m^2 IV on days 1, 8 & 15 Cycled every 28 days Premedication w/ corticosteroids, Diphenhydramine & H2-antagonist is required for all patients	
Paclitaxel (Conventional)	175 mg/m^2 IV infusion over 3 hrs *Cycled every 21 days* ***or*** 80 mg/m^2 IV infusion over 1 hr wkly Premedication w/ corticosteroids, Diphenhydramine & H2-antagonist is required for all patients	
Tegafur[1]	800-1200 mg/kg/day PO x 6 wk	

[1]Combination w/ Uracil is available. Please see MIMS for specific prescribing information.

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Dosage Guidelines

MONOTHERAPY AGENTS FOR RECURRENT OR METASTATIC BREAST CANCER

CYTOTOXIC CHEMOTHERAPY (CONT'D)

Drug	Dosage	Remarks
Vinblastine	3.7 mg/m^2 IV inj Dose may be increased by 1.8 mg/m^2 at wkly intervals until desired effect is achieved or total number of leucocytes has decreased to 3000/mm^3 **Max dose:** 18.5 mg/m^2	**Special Instructions (Cont'd)** **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 25 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 25 **Tegafur** • Use w/ caution in patients w/ bone marrow depression, hepatic or renal disorders, infectious diseases, GI ulcer or hemorrhage, abnormal glucose tolerance, varicella **Vinblastine** • If leukopenia occurs, monitor patients carefully for infection until WBC count returns to normal • Do not inject into an extremity w/ impaired circulation • Avoid in patients w/ leukopenia or bacterial infection **Vincristine** • Give prophylaxis for constipation • Use w/ caution in patients w/ hepatic impairment & pre-existing neuromuscular disease **Vinorelbine** • Use w/ caution in patients w/ ulcerated skin or cachexia • Only used for IV infusion
Vincristine	0.4-1.4 mg/m^2 BSA IV wkly	
Vinorelbine	25 mg/m^2 IV wkly In combination therapy, dose may be the same but frequency reduced (eg day 1 & 8 or day 1 & 5 every 3 wk)	

TARGETED CANCER THERAPY

Drug	Dosage	Remarks
Trastuzumab emtansine	3.6 mg/kg IV infusion every 3 wk until disease progression or unacceptable toxicity **1st infusion:** Over 90 min, observe patient during infusion & for at least 90 min for infusion-related reactions **Subsequent infusions:** Over 30 min if prior infusion well tolerated	**Adverse Reactions** • GI effects (dry mouth, abdominal pain, N/V, diarrhea, constipation); CNS effects (myalgia, arthralgia, musculoskeletal pain, dizziness, peripheral neuropathy, headache, insomnia); Hematological effects (anemia, thrombocytopenia); Metabolic effects (increased transaminases, hypokalemia); Other effects (pyrexia, asthenia, fatigue, dyspnea, cough, epistaxis, rash, hemorrhage) **Special Instructions** • Do not administer at doses >3.6 mg/kg • Monitor serum transaminases, bilirubin, & platelet counts prior to initiation & at each dose • Assess LVEF prior to initiation & at regular intervals during treatment • Discontinue if diagnosed w/ interstitial lung diseases or nodular regenerative hyperplasia • Bleeding w/ fatal outcome & peripheral neuropathy has been reported; fetal harm may occur • Perform assessment of HER2 status

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Dosage Guidelines

COMBINATION THERAPY FOR RECURRENT OR METASTATIC BREAST CANCER

COMBINATION THERAPY REGIMENS

Drug	Dosage	Remarks
Cyclophosphamide + Doxorubicin + 5-Fluorouracil	**Cyclophosphamide:** 100 mg/m^2 PO on days 1-14 **Doxorubicin:** 30 mg/m^2 IV on days 1 & 8 **5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 Cycled every 28 days	<u>**Adverse Reactions**</u> **Bevacizumab** • GI effects (GI perforation, diarrhea, abdominal pain); Respiratory effects (pulmonary hemorrhage/hemoptysis); CV effects (arterial thromboembolism, hypertension); Other effects (fatigue, asthenia) **Capecitabine** • See Capecitabine on page 27 **Cyclophosphamide** • See Cyclophosphamide on page 23 **Docetaxel** • See Docetaxel on page 23 **Doxorubicin** • See Doxorubicin on page 23 **Epirubicin** • See Epirubicin on page 23 **Fluorouracil** • See Fluorouracil on page 23 **Gemcitabine** • See Gemcitabine on page 27 **Lapatinib** • GI effects (N/V, diarrhea, abdominal pain, stomatitis, dyspepsia); Dermatologic effects (rash, palmar-plantar erythrodysesthesia); Hepatic effects (elevated liver enzymes & total bilirubin level); Other effects (dyspnea, anemia, fatigue, back pain) **Methotrexate** • See Methotrexate on page 24 **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 24 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 24
Doxorubicin + Cyclophosphamide	**Doxorubicin:** 60 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 Cycled every 21 days	
Cyclophosphamide + Methotrexate + 5-Fluorouracil	**Cyclophosphamide:** 100 mg/m^2 PO on days 1-14 **Methotrexate:** 40 mg/m^2 IV on days 1 & 8 **5-Fluorouracil:** 600 mg/m^2 IV on days 1 & 8 Cycled every 28 days	
Cyclophosphamide + Epirubicin + 5-Fluorouracil	**Cyclophosphamide:** 400 mg/m^2 IV on days 1 & 8 **Epirubicin:** 50 mg/m^2 IV on days 1 & 8 **5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 Cycled every 28 days	
Paclitaxel + Gemcitabine	**Paclitaxel:** 175 mg/m^2 IV infusion over 3 hrs on day 1 **Gemcitabine:** 1250 mg/m^2 IV on days 1 & 8 (following Paclitaxel on day 1) Cycled every 21 days	
Docetaxel + Capecitabine	**Docetaxel:** 75 mg/m^2 IV on day 1 **Capecitabine:** 950 mg/m^2 PO 12 hrly on days 1-14 Cycled every 21 days	
5-Fluorouracil + Doxorubicin + Cyclophosphamide	**5-Fluorouracil:** 500 mg/m^2 IV on days 1 & 8 or days 1 & 4 **Doxorubicin:** 50 mg/m^2 IV on day 1 **Cyclophosphamide:** 500 mg/m^2 IV on day 1 Cycled every 21 days	

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Dosage Guidelines

COMBINATION THERAPY FOR RECURRENT OR METASTATIC BREAST CANCER

COMBINATION THERAPY REGIMENS (CONT'D)

Drug	Dosage	Remarks
Paclitaxel + Bevacizumab	**Paclitaxel:** 90 mg/m^2 IV infusion over 1 hr on days 1, 8 & 15 **Bevacizumab:** 10 mg/kg IV on days 1 & 15 Cycled every 28 days	**Adverse Reactions (Cont'd)** **Pertuzumab** • See Pertuzumab on page 26 **Trastuzumab** • See Trastuzumab on page 24 **Vinorelbine** • See Vinorelbine on page 28 **Special Instructions** **Bevacizumab** • Discontinue in patients who develop GI perforation, grade 3 or 4 bleeding, arterial thromboembolic events (including CVA, TIA, MI), uncontrolled hypertension • Should not be used in patients w/ recent pulmonary hemorrhage/hemoptysis • Monitor BP; preexisting hypertension should be adequately controlled prior to initiating therapy w/ Bevacizumab **Capecitabine** • See Capecitabine on page 28 **Cyclophosphamide** • See Cyclophosphamide on page 24 **Docetaxel** • See Docetaxel on page 24 **Doxorubicin** • See Doxorubicin on page 24 **Epirubicin** • See Epirubicin on page 25 **Fluorouracil** • See Fluorouracil on page 25 **Gemcitabine** • See Gemcitabine on page 29
Lapatinib + Trastuzumab	**Lapatinib:** 1000 mg/day PO daily **Trastuzumab:** 4 mg/kg IV (loading dose) on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV (loading dose) on day 1 followed by 6 mg/kg IV every 21 days	
Capecitabine + Trastuzumab	**Capecitabine:** 1000-1250 mg/m^2 PO 12 hrly on days 1-14 *Cycled every 21 days* **Trastuzumab:** 4 mg/kg IV (loading dose) on day 1 followed by 2 mg/kg IV wkly or **Trastuzumab:** 8 mg/kg IV (loading dose) on day 1 followed by 6 mg/kg IV every 21 days	
Capecitabine + Lapatinib	**Capecitabine:** 1000 mg/m^2 PO 12 hrly on days 1-14 **Lapatinib:** 1250 mg PO once daily on days 1-21 Cycled every 21 days	
Epirubicin + Cyclophosphamide	**Epirubicin:** 75 mg/m^2 IV on day 1 **Cyclophosphamide:** 600 mg/m^2 IV on day 1 Cycled every 21 days	
Pertuzumab + Trastuzumab + Docetaxel	**Pertuzumab:** 840 mg IV on day 1 followed by 420 mg IV **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV **Docetaxel:** 75-100 mg/m^2 IV on day 1 Cycled every 21 days	

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Dosage Guidelines

COMBINATION THERAPY FOR RECURRENT OR METASTATIC BREAST CANCER

COMBINATION THERAPY REGIMENS (CONT'D)

Drug	Dosage	Remarks
Pertuzumab + Trastuzumab + Paclitaxel	**Pertuzumab:** 840 mg IV on day 1 followed by 420 mg IV *Cycled every 21 days* **Trastuzumab:** 4 mg/kg IV on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV *Cycled every 21 days* **Paclitaxel:** 80 mg/m^2 IV on day 1 wkly ***or*** **Paclitaxel:** 175 mg/m^2 IV on day 1 Cycled every 21 days	**Special Instructions (Cont'd)** **Lapatinib** • Use w/ caution in patients w/ hepatic dysfunction, w/ history of or predisposed to left ventricular dysfunction **Methotrexate** • See Methotrexate on page 25 **Paclitaxel (Albumin bound)** • See Paclitaxel (Albumin bound) on page 25 **Paclitaxel (Conventional)** • See Paclitaxel (Conventional) on page 25 **Pertuzumab** • See Pertuzumab on page 26 **Trastuzumab** • See Trastuzumab on page 25 **Vinorelbine** • See Vinorelbine on page 30
Trastuzumab + Paclitaxel	**Trastuzumab:** 4 mg/kg IV on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV every 21 days **Paclitaxel:** 175 mg/m^2 IV on day 1 cycled every 21 days ***or*** **Paclitaxel:** 80-90 mg/m^2 IV on day 1 wkly	
Trastuzumab + Docetaxel	**Trastuzumab:** 4 mg/kg IV on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV every 21 days **Docetaxel:** 80-100 mg/m^2 IV on day 1 cycled every 21 days ***or*** **Docetaxel:** 35 mg/m^2 IV on days 1, 8, & 15 wkly	
Trastuzumab + Vinorelbine	**Trastuzumab:** 4 mg/kg IV on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV every 21 days **Vinorelbine:** 25 mg/m^2 IV on day 1 wkly ***or*** **Vinorelbine:** 30-35 mg/m^2 IV on days 1 & 8 Cycled every 21 days	
Trastuzumab + Capecitabine	**Trastuzumab:** 4 mg/kg IV on day 1 followed by 2 mg/kg IV wkly ***or*** **Trastuzumab:** 8 mg/kg IV on day 1 followed by 6 mg/kg IV every 21 days **Capecitabine:** 1000-1250 mg/m^2 PO 12 hrly on days 1-14 cycled every 21 days	

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Dosage Guidelines

OESTROGENS & PROGESTERONES & RELATED SYNTHETIC DRUGS

Drug	Dosage	Remarks
Conjugated estrogen	**Palliative treatment:** 10 mg PO 8 hrly x 3 mth	**Adverse Reactions** • GI effects (abdominal pain, diarrhea, dyspepsia, nausea); CNS effects (asthenia, back pain, headache, arthralgia, leg cramps, myalgia, depression, dizziness, insomnia, nervousness); Other effects (pharyngitis, rhinitis, upper resp tract infection, pruritus, breast pain, leukorrhea, vag hemorrhage, vag moniliasis, vaginitis) **Special Instructions** • Use w/ caution in patients w/ increased risk of CV disorders or endometrial cancer; dementia, gallbladder disease, hypercalcemia, visual abnormalities, angioedema, elevated BP, hypertriglyceridemia, impaired liver function, hypothyroidism, fluid retention, ovarian cancer; exacerbation of endometriosis, asthma, DM, epilepsy, migraine, porphyria, SLE & hepatic hemangiomas • Avoid in patients w/ undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia or pregnancy, active or history of DVT, pulmonary embolism, arterial thromboembolic disease

TARGETED CANCER THERAPY

Drug	Dosage	Remarks
Everolimus	**In combination w/ Exemestane:** 10 mg PO 24 hrly May be reduced to 5 mg PO 24 hrly	**Adverse Reactions** • GI effects (N/V, diarrhea, dysgeusia); Hematologic effects (anemia, thrombocytopenia); Other effects (anorexia, hypertriglyceridemia, hyperglycemia, hypercholesterolemia, headache, pneumonitis, cough, dyspnea, rash, dry skin, decreased wt) **Special Instructions** • Use w/ caution in patients w/ severe hepatic impairment, new or worsening resp symptoms, oral ulceration, carcinoid tumors • Treat preexisting infection prior to treatment • Monitor renal function, fasting serum glucose level, CBC
Palbociclib	**In combination w/ Letrozole:** 125 mg PO 24 hrly for 21 days followed by 7 days off-treatment	**Adverse Reactions** • GI effects (N/V, diarrhea, stomatitis); Hematologic effects (neutropenia, leukopenia, anemia, thrombocytopenia); Other effects (upper resp tract infection, alopecia, decreased appetite, asthenia, peripheral neuropathy & epistaxis, pulmonary embolism, fatigue) **Special Instructions** • Monitor CBC prior to start of therapy & at the beginning of each cycle on day 14 of the 1st 2 cycles • Monitor for signs & symptoms of infection & pulmonary embolism

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