Taipei Veterans General Hospital Practices Guidelines

Oncology

Breast Cancer

2007.12.11	制定
2008.02.19	第一次修訂
2009.07.28	第二次修訂
2010.02.09	第三次修訂
2012.05.18	第四次修訂
2013.06.21	第五次修訂
2014.07.11	第六次修訂
2015.03.13	第七次修訂
2016.05.27	第八次修訂
2017.09.08	第九次修訂
2018.09.20	第十次修訂
2019.08.16	第11次修訂
2020.07.31	第12次修訂
2021.10.29	第13次修訂
2022.09.23	第14次修訂

Summary of Guidelines Updated Changes (2022)

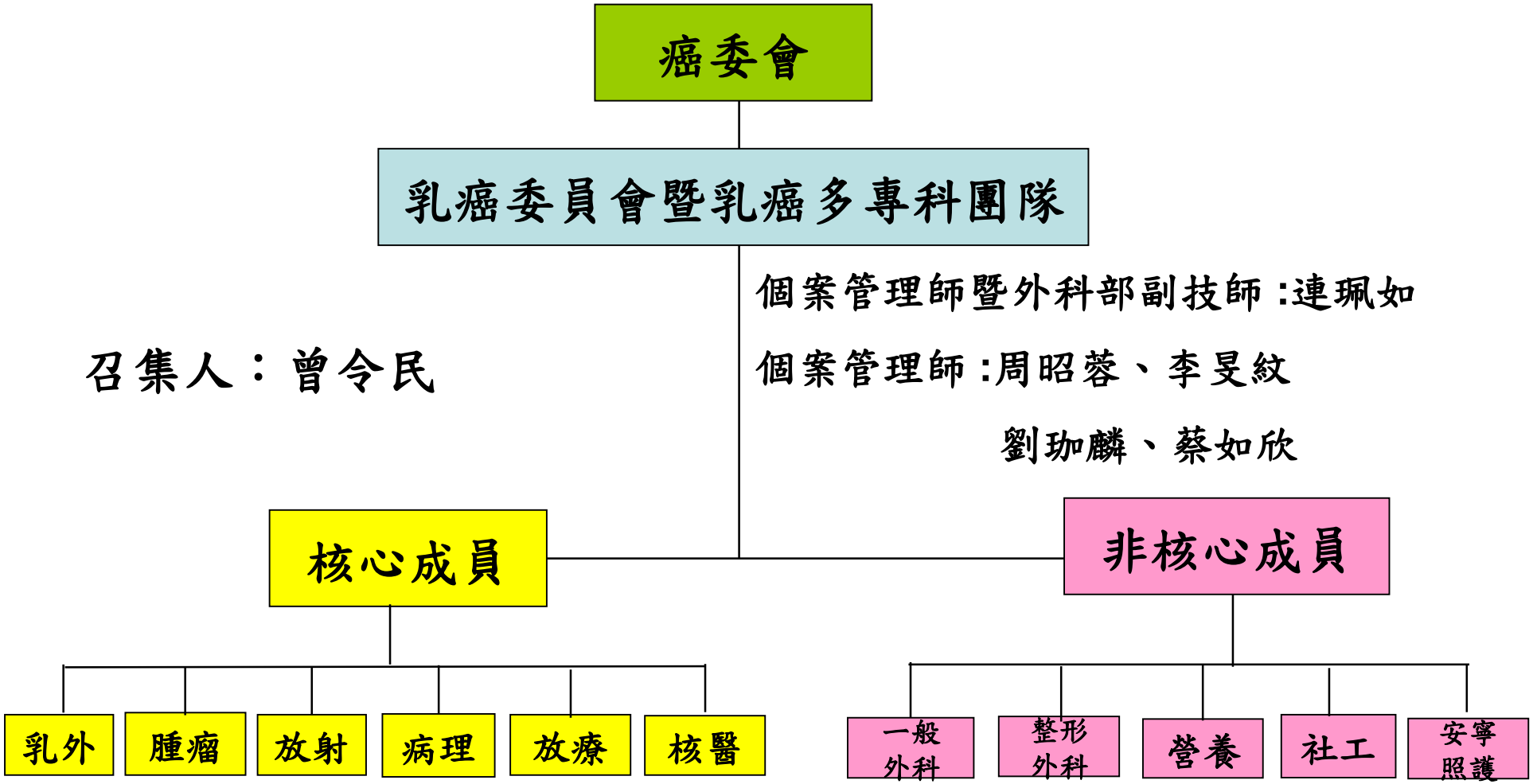
- Slide 56-57: add” Adjuvant S-1 (TS-1) for hormone receptor-positive and HER2 negative moderate/high–risk primary breast cancer-1 and -2”
- Slide 72: add”Trastuzumab deruxtecan (T-DXd)(self-pay) for HER2 IHC 1+ or 2+/ISH negative.”
- Slide 74: add” Trastuzumab deruxtecan (T-DXd) (self-pay)(preferred second line)”
- Slide 82-83、85-89”: update Radiothreapy.

Table of Content

Multidisciplinary Team

- **Surgical Oncology specialized in Breast Cancer**
- **Medical Oncology**
- **Radiation Oncology**
- **Pathology**
- **Diagnostic Radiology**
- **Specialized Nursing Care**
- **Social Workers**
- **Nutritional Support**

臺北榮總乳癌委員會暨乳癌多專科團隊組織架構



臺北榮總乳癌多專科團隊核心人員

乳房外科	曾令民	黃其晟	蔡宜芳	林燕淑	陳彥蓁
乳房外科暨整型外科	馮晉榮				
腫瘤內科	劉峻宇	趙大中	賴峻毅		
放射診斷	王甄	賴亦貞			
病理	許志怡				
放射治療	蕭正英	黃品逸	賴宜君	賴姿妤	
核醫	姚珊汎				

Pathology

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

- **In situ Carcinomas**

  Ductal carcinoma in situ

  Lobular carcinoma in situ

  Paget's disease

- **Invasive carcinomas**

Ductal	Papillary
(Invasive breast carcinoma of no special type)	Micropapillary
Lobular	Metaplastic
Mucinous	Adenoid cystic
Tubular	Secretory
Cribriform	Inflammatory
Carcinoma with apocrine differentiation	

Noninvasive carcinoma (WHO 2019)

- **Ductal carcinoma in situ**
- **Lobular carcinoma in situ**
- **Paget disease without invasive carcinoma**

Invasive carcinoma (WHO 2019)

- **Invasive ductal carcinoma (Invasive breast carcinoma of no special type)**
- **Invasive lobular**
- **Mucinous**
- **Tubular**
- **Cribriform**
- **Carcinoma with apocrine differentiation**
- **Metaplastic**
- **Others (Adenoid cystic, Secretory, Micropapillary, Mucinous cystadenocarcinoma…..)**

Mixed type carcinoma (WHO 2019)

A mixture of invasive breast carcinoma-no special type (IBC-NST) and a special subtype

- Special type (10-90%)

  → Mixed IBC-NST and special subtype carcinoma
- Special subtype < 10%

  → IBC-NST
- Special subtype > 90%

  → Special subtype

Lymphovascular invasion

(Rosen, Cancer, 1983; 18:215-32)

- Lymphovascular invasion (LVI) must be diagnosed outside the border of the invasive carcinoma. (most within 0.1 cm of the edge)
- Tumor emboli usually do not conform exactly to the contours of the space in which they are found. (retraction artifact of ca have exactly same shape)
- Endothelial cell nuclei should be seen in the cells lining the space
- Lymphatics are often found adjacent to blood vessels and often partially encircle a blood vessel.
- LVI may be seen in stroma between uninvolved lobules and can sometimes be mistaken for DCIS

Extensive intraductal carcinoma (component) (EIC)

- Invasive Ca with $\geq$ 25% DCIS component in it and DCIS present outside the invasive Ca
- Ca that are primarily intraductal with small foci of invasion (~10 mm or less)
- EIC is associated with an increased risk of local recurrence when the surgical margins are not evaluated or focally involved

Ductal carcinoma in situ

(Consensus conference on classification of DCIS, Hum Pathol. 1997 Nov)

- **Nuclear grade**
  1. monotonous, 1.5-2× RBC, dispersed chromatin, only occasional nucleoli
  2. not 1, 3
  3. marked pleomorphic nuclei, > 2.5 × RBC, coarse chromatin, prominent or multiple nucleoli
- **Necrosis**
- **Architectural pattern**
  - Comedo, Cribriform, Papillary, Micropapillary, Solid

Lobular carcinoma in situ (LCIS)

- Classic/typical LCIS Need not quantified the size
- Classic/typical LCIS Need not evaluation of margin (often multifocal and bilateral)
- but with high-grade nuclei and/or necrosis, size and margin are needed (clinicians may choose to treat such cases as DCIS).

Lobular neoplasia (LN) (WHO 2019)

- **Atypical lobular hyperplasia (ALH)**

  <1/2 involvement by the characteristic cells
- **Classic lobular carcinoma in situ (LCIS)**

  Dyscohesive cells filling and expanding >1/2 of the acini in a terminal duct lobular unit.
- **Variants of LCIS**

  high grade nuclei (pleomorphic LCIS)

  confluent mass-like architecture (florid LCIS)
- **E-cadherin (-)**

Invasive lobular carcinoma (WHO 2019)

Noncohesive cells individually dispersed or arranged in a single-file linear pattern in a fibrous stroma

- **classic pattern**
  - Small cells, lack cohesion, individually dispersed in fibrous tissue or arranged in single file linear cords
- **variants**
  - Solid pattern
    small cells grow in sheets, higher frequency of mitoses
  - Alveolar pattern
    globular aggregates of at least 20 cells
  - Pleomorphic pattern
    Marked pleomorphism, > 4× lymphocytes and a higher mitotic count
    may apocrine or histiocytoid differentiation and have signet ring cells
  - Tubulolobular pattern
    mixed tubular and lobular growth pattern

Mucinous carcinoma (MC) (WHO 2019)

- **Tumor clusters suspended in pools of extracellular mucin partitioned by delicate fibrous septa containing capillary blood vessels**
- **low to intermediate nuclear grade**
- **Pure MC requires a mucinous component of > 90%**
  - mixed MC has 10–90%
  - A mucinous component of < 10% should be mentioned
- **MC with micropapillary pattern**
  - younger age, more lymph node metastasis

Carcinoma with apocrine differentiation (WHO 2019)

- **cytological features of apocrine differentiation**
  - prominent nucleoli, marked or moderate atypia
  - Abundant eosinophilic, granular, or foamy cytoplasm
  - Apocrine morphology may in some special subtypes of carcinomas
- **Usually GCDFP-15 (+), androgen receptor (+)**
- **Usually ER (–) and PR(–)**

Tubular Carcinoma (WHO 2019)

- A low grade breast carcinoma
- >90% well differentiated angular tubular structures
- open lumina lined by a single layer of cells
- Basement membrane absent
- Myoepithelial cells absent
- ER-positive and HER2-negative
- favorable prognosis

Cribriform carcinoma (WHO 2019)

- **> 90% invasive cribriform pattern**
- **low-grade nuclei and sparse mitosis (grade 1)**
- **ER-positive and HER2-negative**
- **Good prognosis**

Neuroendocrine neoplasms (MENs) (WHO 2019)

- if neuroendocrine histological features and neuroendocrine marker expression are not distinct or uniform enough to classify the tumour as a NEN
  → Invasive breast carcinoma with neuroendocrine differentiation
- Mucinous carcinoma, Solid papillary carcinoma may express neuroendocrine markers, and they should not be classified as NET or NEC

- **Neuroendocrine tumor (NET)**
  - an invasive tumour with low/intermediate-grade neuroendocrine morphology
  - diffuse, uniform immunoreactivity for neuroendocrine markers
  - Solid nests and trabeculae of spindle, plasmacytoid, or polygonal cells with granular cytoplasm separated by delicate fibrovascular stroma
  - Ribbons, cords, and rosettes are not necessarily features
  - Using Nottingham grading system, the majority of NETs are G1 or G2.
- **Neuroendocrine carcinoma (NEC)**
  - high-grade neuroendocrine morphology (small cell or large cell)
  - similar to those of small cell NEC and large cell NEC of the lung
  - diffuse, uniform immunoreactivity for neuroendocrine markers

Metaplastic Carcinoma (WHO 2019)

- **An invasive breast cancer with atypical squamous, spindle cell, and/or mesenchymal/matrix-producing differentiation**
- **unequivocal expression of (high-molecular-weight) cytokeratins and/or p63**
- **A heterogeneous group of tumors**
  - Low-grade adenosquamous carcinoma
  - Fibromatosis-like metaplastic carcinoma
  - Spindle cell carcinoma
  - Squamous cell carcinoma
  - Metaplastic carcinoma with heterologous mesenchymal differentiation
  - Mixed metaplastic carcinoma

Estrogen & Progesterone Receptor

(ASCO/CAP Guideline Recommendations 2020)

Immunohistochemical stain

- **Estrogen receptor (ER)**
  - –Positive (>10%)
  - –Low positive (1%-10%)
  - –Negative (<1%)

- **Progesterone Receptor (PR)**
  - –Positive (≥1%)
  - –Negative (<1%)

HER-2/Neu

(ASCO/CAP Guideline Recommendations 2018)

- **Immunohistochemical stain (IHC)**
  - Negative (0) : No staining, or <=10% incomplete faint staining
  - Negative (1+): Incomplete faint membrane staining >10% tumor
  - Equivocal(2+): Weak/moderate complete membrane staining >10%
  - Positive (3+): Complete intense membrane staining >10% tumor
  - Indeterminate: technical issues prevent a result;
    conditions may include inadequate specimen handling, artifacts that make interpretation difficult or analytic testing failure

- **Her2/neu gene amplification**
  - Positive: Her2/CEP17 $\geq$ 2.0 and average Her2 $\geq$ 4.0/cell or
    Average Her2 $\geq$ 6.0/cell and Her2 IHC (2+).
  - Negative: Her2/CEP17 < 2.0 and average Her2 < 4.0/cell.
  - Other ISH results with Her2 IHC (2+) are Her2 negative.
  - Indeterminate: technical issues prevent a result; conditions may include inadequate specimen handling, artifacts that make interpretation difficult or analytic testing failure.

Pretreatment work-ups

- **History and physical exam**
- **CBC (including platelets), PT/APTT**
- **Liver and renal function tests and alkaline phosphatase**
- **Hepatitis B and hepatitis C virus markers.**
- **Chest X-rays**
- **Diagnostic bilateral mammogram, breast ultrasound as necessary**
- **Pathology review if indicated, include:**
  - Estrogen/progesterone receptor (ER/PR) status
  - HER2 status
- **Special studies for patients receiving neoadjuvant chemotherapy or symptom guided studies**
  - Whole body bone scan
  - Chest CT scan

Pretreatment work-ups

- **Patients who will receive anthracyclines and/or anti-HER2 agents: Radionuclide studies or cardiac echocardiography for ejection fraction of left cardiac ventricle**
- **Optional studies**
  - Tumor markers: CEA, CA-153
  - Abdominal ultrasound
  - Whole body bone scan
  - Breast MRI
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - PET/CT scan
  - Bone mineral density

Recommended follow-up studies for patients with early breast cancer after initial treatment (except endocrine therapy) (1)

- **Adjustment by doctors' and patients' consideration, risk, and previous studies results, etc.**
- **Clinical OPD visit and physical examination:**
  - First 2-3 years: q3-6 months
  - Following 2-3 years: q6-12 months
  - After 5 years: q6-12 months
- **Patients who receive anthracyclines and/or anti-HER2 agents: Radionuclide studies or cardiac echocardiography for ejection fraction of left cardiac ventricle, q2-q3m, at least to the end of anthracyclines and/or anti-HER2 agents treatment.**

Recommended follow-up studies for patients with early breast cancer after initial treatment (except endocrine therapy) (2)

- **Other optional studies:**
  - CBC (including platelets)
  - Liver and renal function tests and alkaline phosphatase
  - Chest X-rays
  - Diagnostic bilateral mammogram, breast ultrasound
  - Abdominal ultrasound
  - Tumor markers: CEA, CA-153
  - Whole body bone scan

Principles of surgery

- Lumpectomy with surgical axillary staging (breast conserving surgery)
- Total or NAC/skin sparing mastectomy with surgical axillary staging (modified raical mastectomy) ± reconstruction
- Sentinel lymph node biopsy is preferred method to access the pathologic status of axillary lymph nodes for patients with clinical stage I or II breast cancers.
- Women who undergo mastectomy are appropriate candidates for breast reconstruction.

Margin status in infiltrating carcinoma (1)

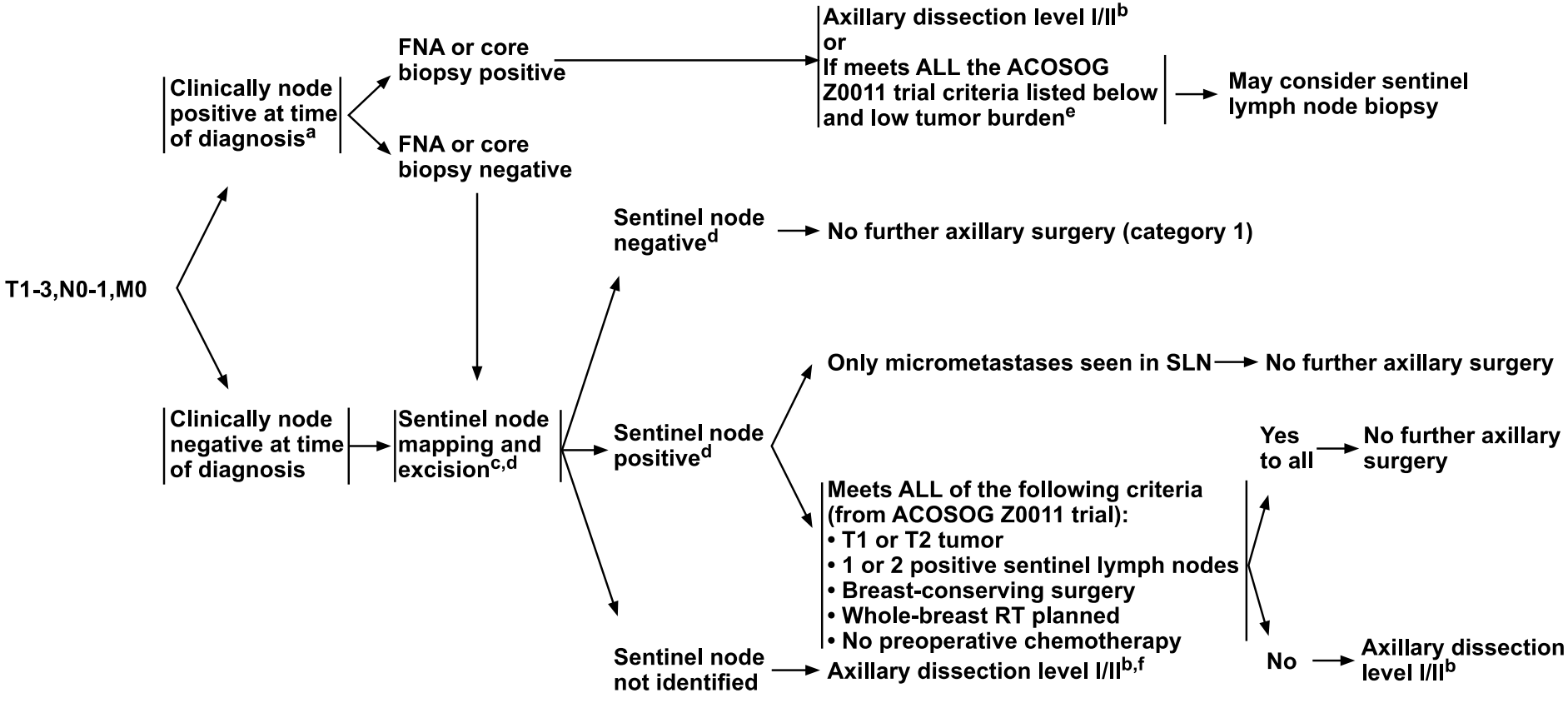
- **The use of breast conserving therapy is predicated on achieving a pathologically negative margin of resection.**
  - Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy.
  - If re-excision is technically feasible to allow for breast conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or reexcision of the entire original excision cavity.
  - If multiple margins remain positive, mastectomy may be required for optimal local control.

Margin status in infiltrating carcinoma (2)

- **It may be reasonable to treat selected cases with breast conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component.**
  - For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

- **Margins should be evaluated on all surgical specimens from breast conserving surgery. Requirements for optimal margin evaluation include**:
  - Orientation of the surgical specimens
  - Description of the gross and microscopic margin status
  - Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

Axillary lymph node staging



[a] Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy.

[b] See Axillary Lymph Node Staging (BINV-E).

[c] Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.

[d] Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.

[e] Low tumor burden in the axilla means nodal disease that 1) is image-detected disease not apparent on clinical exam; and 2) appears to be limited to one or two axillary nodes.

[f] For patients with clinically negative axilla who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

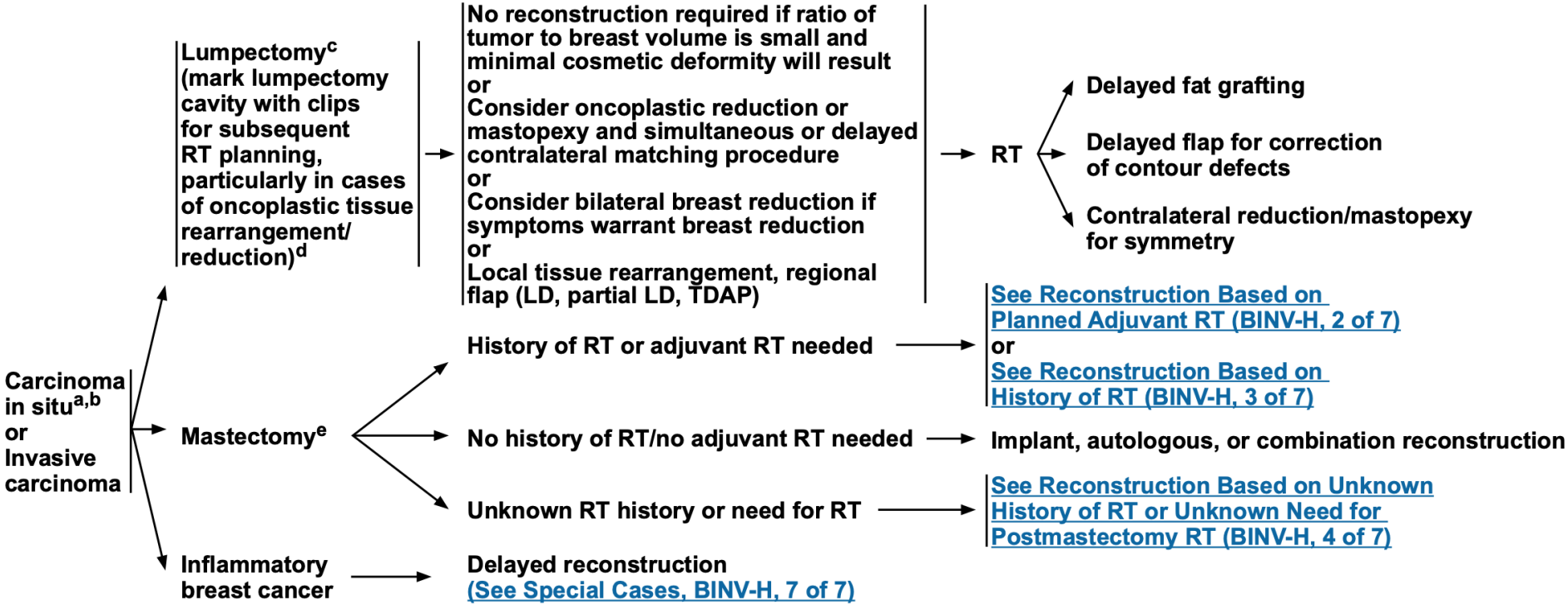
Axillary lymph node staging

- SLNB should be performed and is the preferred method of axillary lymph node staging if the patient is an appropriate SLNB candidate.
- In the absence of definitive data demonstrating superior survival, the performance of axillary staging may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic and/or radiation therapy is unlikely to be affected, the elderly, or those with serious comorbid conditions.
- Level III dissection to the thoracic inlet should be performed only in cases with gross disease in level II and/or lll.
- In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I/II).

Principle of breast reconstruction after mastectomy

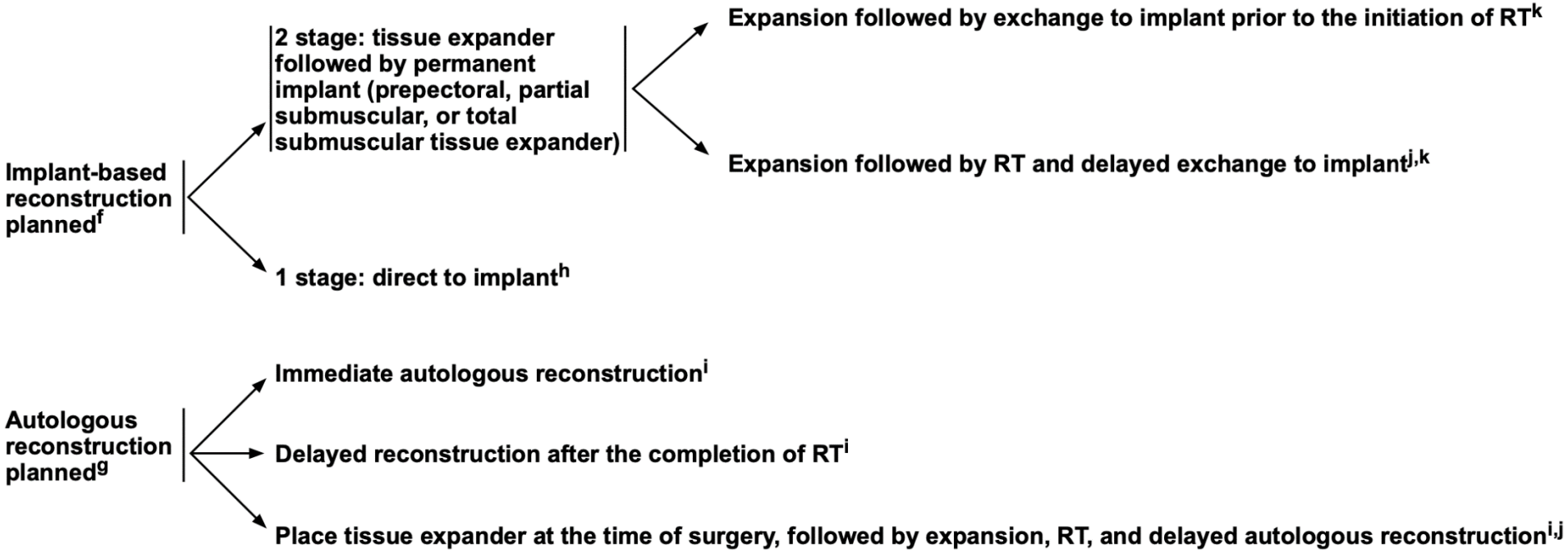
- **Reconstruction using breast implants, autologous tissue (“flaps) or a combination of the two (e.g., latissimus / implant composite recosntructions).**
- **Breast reconstruction for mastectomy can be performed at the same time as mastectomy (“immediate”) or at some time following the completion of cancer treatment (“delayed”).**
- **Skin sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and to perform a resections that achieves appropriate surgical margins. Post-mastectomy radiation should be applied in cases treated by skin sparing mastectomy.**
- **When post-mastectomy radiation is required, delayed reconstruction is generally preferred after completion of radiation therapy in autologous tissue reconstruction, because of reported loss in reconstruction cosmesis.**
- **When implant reconstruction is used, immediate rather than delayed reconstruction is preferred to avoid tissue expansion of radiated skin flaps.**
- **Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis and implant exposure.**
- **Nipple areolar reconstruction should be offered to patients if the nipple-areolar complex (NAC) has been removed as part of their cancer treatment. Various techniques are available for nipple reconstruction. 3-D tattooing can be offered to patients as an option for NAC reconstruction.**
- **There exists an association between certain types of textured breast implants and BIA-ALCL. The risk appears to vary based on the method of texturing. Patients with a past or current history of textured implants should follow up with their reconstructive surgeon.**

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY



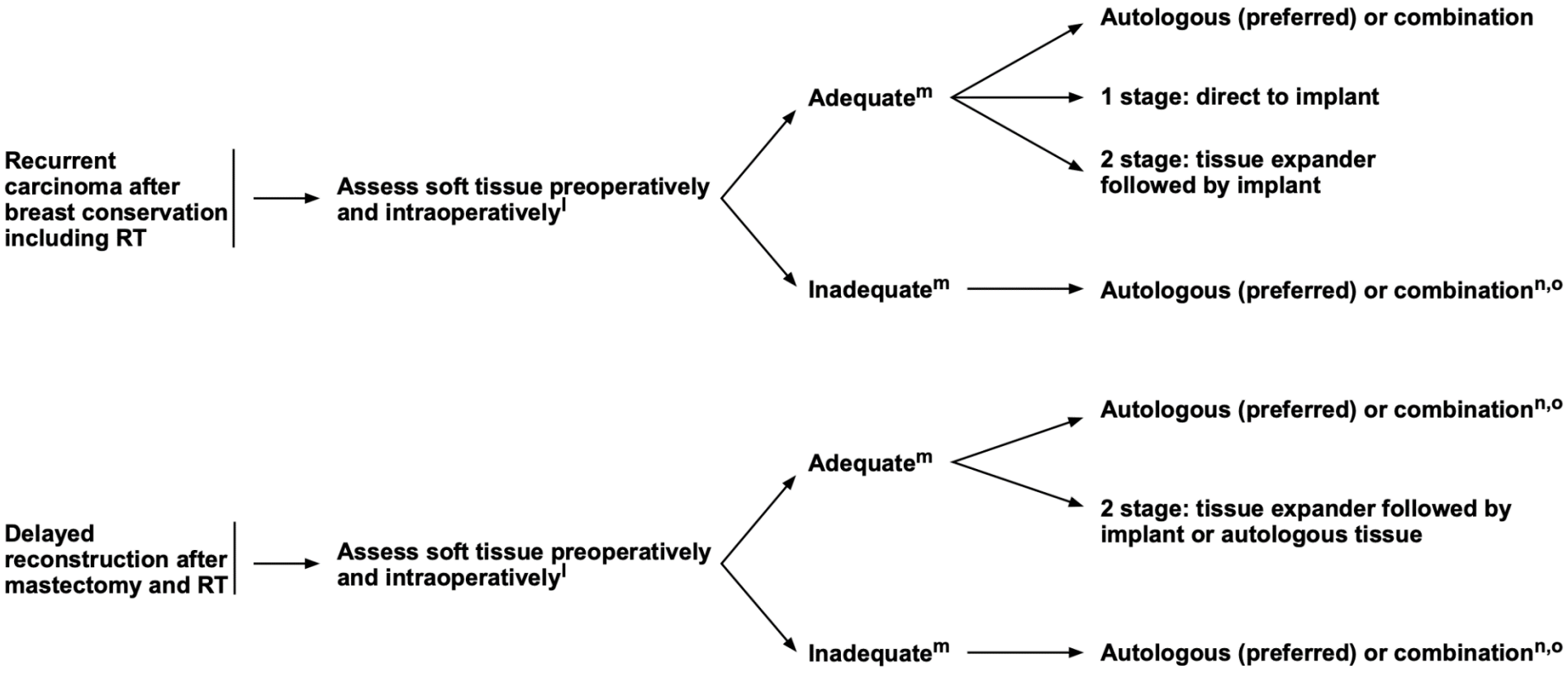
PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON PLANNED ADJUVANT RT[a,b]



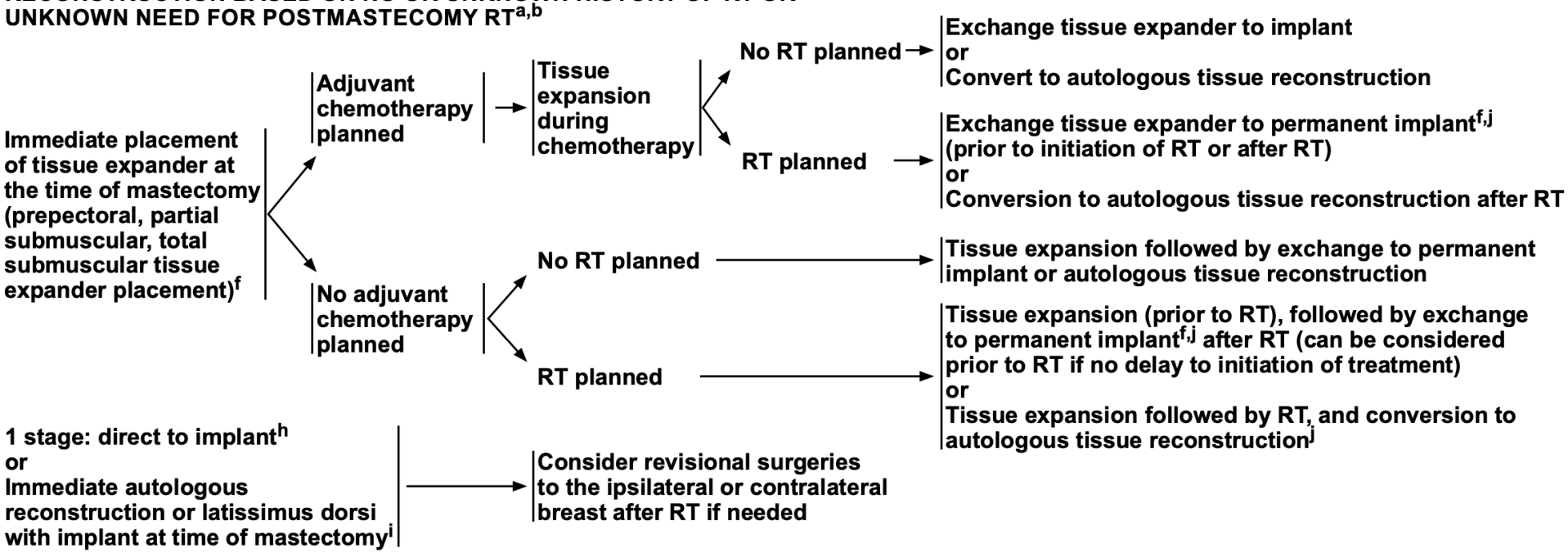
PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON HISTORY OF RT[a,b]



PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON NO OR UNKNOWN HISTORY OF RT OR UNKNOWN NEED FOR POSTMASTECOMY RT[a,b]



TNM Staging System:
AJCC Cancer Staging, Eighth Edition (2017)

Primary tumor (T)

AJCC Cancer Staging Manual, 8th ed. (2017)

Primary Tumor (T) The T category of the primary tumor is defined by the same criteria regardless of whether it is based on clinical or pathological criteria, or both. The T category is based primarily on the size of the invasive component of the cancer. The maximum size of a tumor focus is used as an estimate of disease volume. The largest contiguous dimension of a tumor focus is used, and small satellite foci of noncontiguous tumor are not added to the size. The cellular fibrous reaction to invasive tumor cells is generally included in the measurement of a tumor prior to treatment; however, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the residual tumor volume. The clinical size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities, such as mammography, ultrasound, and MR imaging) and pathological findings (gross and microscopic measurements). Clinical tumor size (cT) should be based on the clinical findings that are judged to be most accurate for a particular case, although it may still be somewhat inaccurate because the extent of some breast cancers is not always apparent with current imaging techniques and because tumors are composed of varying proportions of noninvasive and invasive disease, which these techniques are currently unable to distinguish. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification the size should be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 4.9 mm is reported as 5 mm, or a size of 2.04 cm is reported as 2.0 cm (20 mm). The exception to this rounding rule is for a breast tumor sized between 1.0 and1.4 mm. These sizes are rounded up to 2 mm, because rounding down would result in the cancer's being categorized as microinvasive carcinoma (T1mi) defined as a size of 1.0 mm or less.

TNM Staging System:

T Stage

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ in the underlying breast parenchyma.
T1	Tumor ≤ 20mm in greatest dimension
T1mic	Tumor ≤ 1mm in greatest dimension
T1a	Tumor >1mm but ≤5mm in greatest dimension
T1b	Tumor >5mm but ≤10mm in greatest dimension
T1c	Tumor >10mm but ≤20mm in greatest dimension
T2	Tumor >20mm but ≤50mm in greatest dimension
T3	Tumor >50mm in greatest dimension
T4	Tumor of any size with direct extension to chest wall and/or skin (ulceration or skin nodules)

Note: Invasion to the dermis alone dose not qualify as T4

T4a	Extension to chest wall, not including pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema(including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

N Stage

Clinical

Nx	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically detected level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

TNM Staging System (cont'd)

Pathologic (pN)

pNX Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)

pN0 No regional lymph node metastasis identified histologically

pN0(i－) No regional lymph node metastasis histologically, negative IHC

pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2mm (detected by H&E or IHC including ITC)

pN0(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)

pN0(mol+) Positive molecular findings(RT-PCR), but no regional lymph node metastases detected by histology or IHC

pN1 Micrometastases; or metastases in 1－3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected

pN1mi Micrometastases (greater than 0.2 mm and /or more than 200 cells, but none greater than 2.0 mm)

pN1a Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0mm

pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN1c Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastases in 4 to 9 axillary lymph nodes, or in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastasis

pN2a Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

pN2b Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastases

pN3 Metastases in 10 or more axillary lymph nodes, or in infraclavicular (level III axillary) lymph nodes, or in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary) lymph nodes

pN3b Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN3c Metastases in ipsilateral supraclavicular lymph nodes

TNM Staging System (cont'd)-Distant metastasis (M):

- **MX:**

  Presence of distant metastasis cannot be assessed

- **M0:**

  No distant metastasis

- **cM0(i+):**

  No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2mm in a patient without symptoms or signs or metastases

- **M1:**

  Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2mm

STAGE GROUPING

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	**Tis**	**N0**	**M0**
Stage IA	**T1***	**N0**	**M0**
Stage IB	**T0**	**N1mi**	**M0**
	T1*	**N1mi**	**M0**
Stage IIA	**T0**	**N1****	**M0**
	T1*	**N1****	**M0**
	T2	**N0**	**M0**
Stage IIB	**T2**	**N1**	**M0**
	T3	**N0**	**M0**
Stage IIIA	**T0**	**N2**	**M0**
	T1*	**N2**	**M0**
	T2	**N2**	**M0**
	T3	**N1**	**M0**
	T3	**N2**	**M0**
Stage IIIB	**T4**	**N0**	**M0**
	T4	**N1**	**M0**
	T4	**N2**	**M0**
Stage IIIC	**Any T**	**N3**	**M0**
Stage IV	**Any T**	**Any N**	**M1**

*T1 includes T1mi

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

HISTOLOGIC GRADE

GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable)
G2	Intermediate combined histologic grade (moderately favorable)
G3	High combined histologic grade (unfavorable)

- All invasive breast carcinomas with the exception of medullary carcinoma should be graded.
- Nottingham Histologic Score is recommended (Modified Scarff-Bloom-Richardson grading (Elston, Histopathol 1991 19:403-10))

Histologic grade (Nottingham)

- **Tubule formation**
  1 >75%
  2 10-75%
  3 <10%

- **Nuclear Pleomorphism**
  1 small regular (size of normal cell)
  2 moderate increase size (open, vesicular nuclei with visible nucleoli)
  3 marked varied size, nucleoli, chromatin clumping (vesicular with prominent, often multiple nucleoli)

Histologic grade (Nottingham)

- **Mitoses (0.59 mm diameter) (0.44mm)**

1	<10/10 HPF	0-5
2	10-20	6-10
3	>20	>10

grade 1 3-5 points of score
grade 2 6-7
grade 3 8-9

Treatment allocation by therapeutic target and risk categories: adjuvant chemotherapy and endocrine therapy:

- All of the following categories designed for pT > 1 cm (≥T1c)
- pT > 0.5 cm and ≤ 1cm N0M0: individualized therapy (reference as NCCN 2019)
- pT ≤ 0.5cm N0M0: no adjuvant chemotherapy
- Recommend anthracycline (epirubicin)-containing regimens in patients with EF ≥ 50%；when EF < 50%: consider TC instead of EC.

VGH Breast Cancer Phenotype Grouping

VGH Breast Cancer Phenotype Group			
VGH Phenotype Group	HR Status	HER2	Aggressiveness
Luminal A	Strong	-	Low
Luminal B Her2-	Moderate	-	Moderate~High
Luminal B TNB Like	Weak	-	Any
Luminal B Her2+	Positive	+	Any
HER2	Negative	+	Any
Triple Negative	Negative	-	Any

VGH Breast Cancer
Hormonal Status and Aggressiveness Classification

VGH Hormonal Status Classification			
VGH HR Status	ER		PR
Strong	≥50%	&	≥20%
Moderate	Else		
Weak	1~9%	&	1~9%
Negative	<1%	&	<1%

VGH Aggressiveness Classification			
VGH Aggressiveness	HG		MIB-1
High	3	&	≥30%
Moderate	Else		
Low	<3	&	<20%
HG: Histology Grade			

VGH Breast Cancer Systemic Therapy Guideline Table

VGH Breast Cancer Phenotype Group	M0										M1
	N0					N1			N2	N3	Any
	T1a	T1b	T1c	T2	T3-4	T1	T2	T3-4	Any	Any	Any
Luminal A	H	H	H	H	C+H	C+H or H	C+H or H	C+H	C+H	C_DD+H	H or C_Met+H
Luminal B Her2-	H	H	C+H	C+H	C+H	C+H	C+H	C+H	C+H	C_DD+H	C_Met+H
Luimnal B TNB Like	H	H	C+H	C+H	C+H	C+H	C+H	C+H	C+H	C_DD+H	C_Met+H
Luminal B Her2+	H	H	C+T+H	C+T+H	C+T+H	C+T+H	C+T+H	C+T+H	C+T+H	C_DD+T+H	C_Met+T+H
HER2	optional	optional	C+T	C+T	C+T	C+T	C+T	C+T	C+T	C_DD+T	C_Met+T
Triple Negative	optional	optional	C_tnb	C_tnb	C_tnb	C_tnb	C_tnb	C_tnb	C_tnb	C_tnb_DD	C_tnb_Met

Note:

VGH Breast Cancer Phenotype Group dose not take any gene analysis result into consideration. If a gene analysis result is available, an appropriate adjustment could be made accordingly.

H: Hormone Therapy

C+H: Chemotherapy and Hormone Therapy

C+T: Chemotherapy and HER2 Targeted Therapy

C+T+H: Chemotherapy, HER2 Targeted Therapy and Hormone Therapy

C_tnb: Chemotherapy for TNB breast cancer

C_DD: Dose-Dense Chemotherapy

Self-pay

Non Dose-dense regimen as options

Dose-dense regimen as options

Surrogate definitions of intrinsic subtypes of breast cancer

- **Luminal A-like:**

  All of: ER positive and ≧ 50%, PgR positive and ≧ 20 %, grade1 or 2, HER2 negative, Ki-67 'low' (< 20%),
  Recurrence risk 'low' (if available) (oncotype Dx (< 26) or MammaPrint (Symphony) low risk (if available).

- **Luminal B-like:**

  1 Luminal B-like (HER2 negative): ER positive, HER2 negative, and at least one of: Ki-67 'high'(≧ 30 %), PgR 'negative or low(< 20%)', grade3, risk 'high' based on multi-gene-expression assay (if available, such as Oncotype Dx Recurrence score ≥ 31).

  2 Luminal B-like (HER2 positive): ER positive, HER2 over-expressed or amplified, any Ki-67, any PgR

- **HER2 positive (non-luminal):**

  HER2 over-expressed or amplified, ER and PgR negative (< 10%)

- **Triple negative (ductal):**

  ER and PgR negative (< 10%), HER2 negative

Category 1: Node (-) and Luminal A-like disease

A. Adjuvant chemotherapy: No
   –Options: CMF x 6 or E(90)C x 6 or TC x 4 (T self-pay).
B. Adjuvant endocrine therapy: Yes (See Adjuvant endocrine therapy).

Category 2: Node (-) and Luminal B-like disease

A. Adjuvant chemotherapy:
   ① HER2 (-): E(90)C x 6
      –Option: CMF x 6 or TC x 4 (T self-pay).
   ② HER2 (+): Adjuvant chemotherapy + trastuzumab(self-pay)
      – E(90)C x 6 + trastuzumab (self-pay) after EC
      Options: E(90)C x 4 + taxanes (self-pay); add trastuzumab (self-pay) after EC
B. Adjuvant endocrine therapy: Yes (See Adjuvant endocrine therapy).

Category 3: Node (-) and HER2 positive (non-luminal):

A. Adjuvant chemotherapy:

Adjuvant chemotherapy + trastuzumab(self-pay)

- E(90)C x 6 + trastuzumab (self-pay) after EC
- Options:
  - E(90)C x 4 + taxanes (self-pay); add trastuzumab (self-pay) after EC
  - Paclitaxel (self-pay) + trastuzumab (APT)(self-pay) (for T ≤ 2cm*)

B. Adjuvant endocrine therapy for ER/PR 1~10 %: Yes (See Adjuvant endocrine therapy).

* NCCN suggested: APT regimen may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities. APT trail included only 9% of T2 (>2.0 to ≤3.0 cm) patients.

Category 4: Node 1-3 (+) and Luminal disease:

A. Adjuvant chemotherapy:

① HER2 (-): E(90)C x 4 + taxanes (tri-weekly docetaxel x 4)
–Options: E(90)C x 4 + weekly paclitaxel x 12 {self-pay if ER (+)}; consider no chemotherapy (luminal A-like, esp. for metastasis in 1 axillary lymph node)
–Options: RS ≤ 25, no chemotherapy for postmenopausal women[1]

② HER2 (+): add trastuzumab (± pertuzumab, self-pay; ± neratinib for HR(+)[2], self-pay) after EC

B. Adjuvant endocrine therapy: Yes

1.RxPONDER trial, SABCS 2020. NCCN. 2. ExteNET Study, Lancet Oncol. 2017.

Category 5: Node ≧ 4 (+) disease (except triple negative (ductal) disease)

A. Adjuvant chemotherapy:
   ① E(90)C x 4 + taxanes (tri-weekly docetaxel x 4 or weekly paclitaxel x12 (self-pay for ER (+)))
   ② HER2 (+): Add trastuzumab(± pertuzumab, self-pay; ± neratinib for HR (+)[1] , self-pay) after EC
   ③ Options: Dose-dense chemotherapy
   ④ Adjuvant endocrine therapy: for ER and/or PR (+).

1. ExteNET Study, Lancet Oncol. 2017.

Category 6: Triple Negative Disease:

A. Definition: ER 0-9%, PR 0-9%, HER2 (-).
B. Adjuvant chemotherapy: E(90)C x 4 + taxanes (tri-weekly docetaxel x 4 or weekly paclitaxel x12 (self-pay for ER (+)))
C. Options for Node ≧ 4: dose-dense chemotherapy
D. Options after adjuvant chemotherapy: metronomic capecitabine (650mg/m2 bid continuously for 1 year[2])
E. Adjuvant endocrine therapy: for ER ≥1%

2. STSUCC001, ASCO 2020

Adjuvant S-1 (TS-1) for hormone receptor-positive and HER2 negative moderate/high–risk primary breast cancer-1

- **S-1 (TS-1, 20 mg, 25 mg)(self-pay)bid x 14 days/q3w x 1 year**
- **Indications:**
  - With preoperative chemotherapy
  - With preoperative endocrine therapy
  - Without preoperative systemic therapy

With preoperative chemotherapy		
Axillary node metastasis before PST*	Pathological response to PST	Eligibility
Absent	pCR	X
	Non-pCR	O
Present	Regardless of pathological response	O

*pathologically or cytologically proven

With preoperative endocrine therapy		
Axillary node metastasis before PST	Pathological response to PST	Eligibility
Absent	Same as the criteria of patients without PST (based on T, N, Grade, and proliferation marker)	
Present	Regardless of pathological response	O

Axillary node metastasis or lympho-vascular invasion	Histologic grade	Invasion diameter		
		< 2 cm	≥ 2 To < 3 cm	≥ 3 cm
Absent	Grade 1	X	Proliferation marker analysis#	O
	Grade 2	Proliferation marker analysis#	O	O
	Grade 3	O	O	O
Present	O: Eligible regardless of histologic grade and invasion diameter			

#Ki67 labeling index (LI) ≥ 30%, KI67 LI ≥ 14% and Oncotype DX RS ≥ 18
PST = pre-operative systemic therapy

POTENT study. SABCS 2019. Lancet Oncol 2021; 22: 74–84

Adjuvant S-1 (TS-1) for hormone receptor-positive and HER2 negative moderate/high–risk primary breast cancer-2

Starting dose		
Ccr** (before S-1 administration)	BSA (m^2)	Damealily Dose (after meal)
≥ 80 mL/min	< 1.25	80mg (40mg BID)
	1.25 to 1.5	100mg (50mg BID)
	≥ 1.5	120mg (60mg BID)
50-79 mL/min	< 1.25	60mg (morning 20mg, evening 40mg)
	1.25 to < 1.5	80mg (40mg BID)
	≥ 1.5	100mg (50mg BID)

POTENT study. SABCS 2019. Lancet Oncol 2021; 22: 74–84

Representative adjuvant chemotherapy and anti-HER2 regimens:

＊EF < 50%: Consider TC x 4 or 6 (self-pay for node 0-3) instead of EC

1. CMF

A. CivMF: cycled every 21 days.
- –Cyclophosphamide 600 mg/m2 day 1
- –Methotrexate 40 mg/m2 IV day 1
- –5-fluorouracil 600 mg/m2 IV day 1

B. Classical CMF: cycled every 28 days.
- –Cyclophosphamide 100 mg/m2 PO days 1-14
- –Methotrexate 40 mg/m2 IV days 1 & 8
- –5-Fluorouracil 600 mg/m2 IV days 1 & 8

2. E(90)C: cycled every 21 days.

- – Cyclophosphamide 600 mg/m2 IV day 1
- – Epirubicin 90 mg/m2 IV day 1

3. Taxanes:

- –Weekly paclitaxel: 80mg/m2 IV qw x 12 (for ER(-), ER(+) self-pay)
- –Bi-weekly paclitaxel (for dose-dense regimen): 175 mg/m2 IV q2w x 4 (for ER(-), ER(+) self-pay)
- –Tri-weekly docetaxel: 75 mg/m2 IV q3w x 4

4. **Dose-dense:** E(90)C q2w x4 +weekly paclitaxel x12(preferred) or bi-weekly paclitaxel x 4.
5. **TC: cycled every 21 days.**
   – Docetaxel 75 mg/m2 IV day 1
   – Cyclophosphamide 600 mg/m2 IV day 1
6. **Trastuzumab: 4 mg/kg loading, 2 mg/kg/week; or 8mg/kg loading, 6 mg/kg/q3week; x 1 year after anthracycline-based regimens.**
   Option: 9 week or 26 week for patients who self-pay trastuzumab.
7. **Pertuzumab: 840 mg IV day 1 loading, followed by 420 mg IV q3w x1 year**
8. **Paclitaxel + trastuzumab (APT) (self-pay):**
   - Weekly paclitaxel 80 mg/m2 iv day 1 x 12
   - Trastuzumab: 4 mg/kg loading, 2 mg/kg/week; or 8mg/kg loading, 6 mg/kg/q3week; x 1 year (reference: N Engl J Med 2015;372:134-141.)

Adjuvant endocrine therapy:

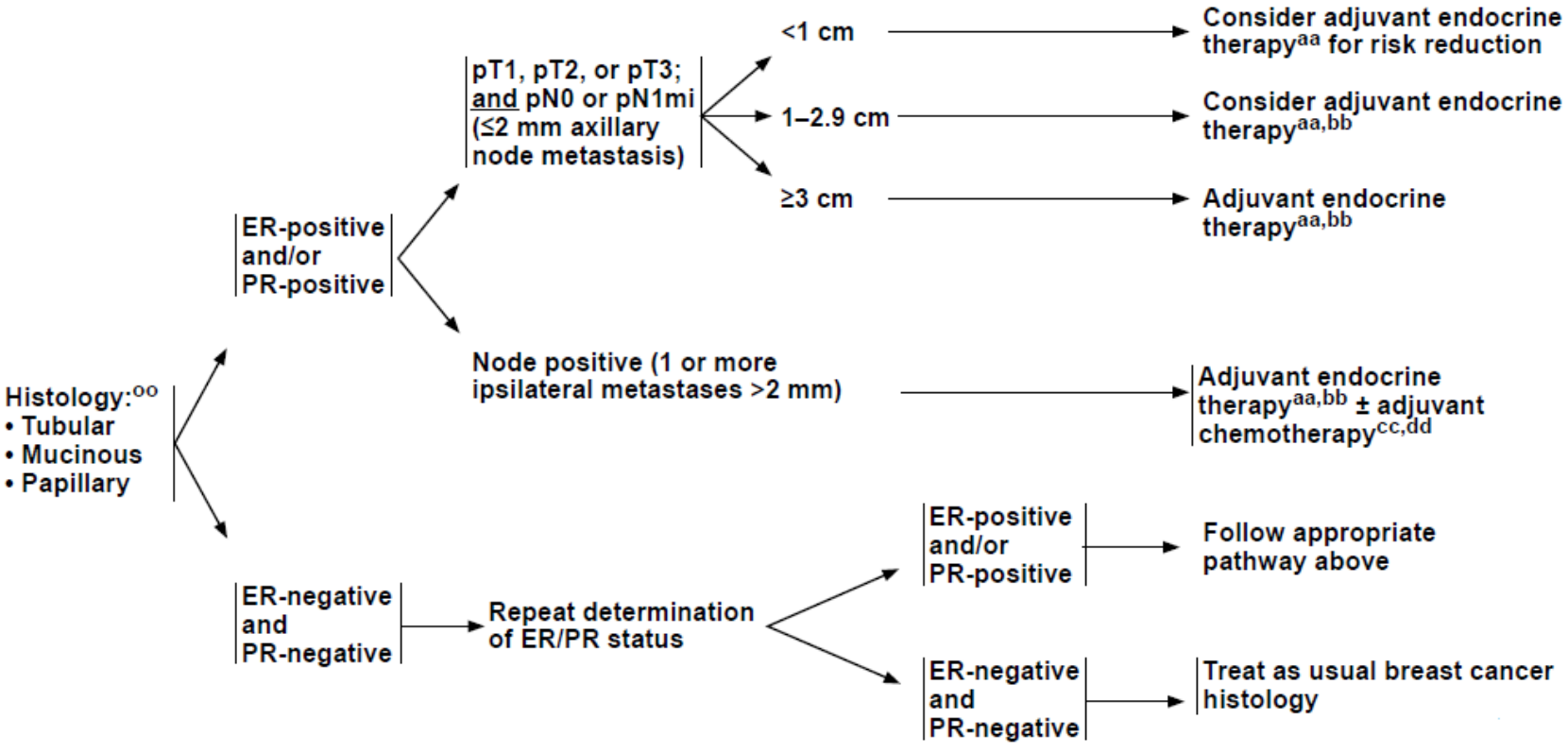
for ER ≥ 1% , or ER 0% and PR ≥ 10%

Recommendation: as NCCN 2021

- Recommend upfront letrozole x 5 years for postmenopausal patients (node (+) and node (-)), and extended use of letrozole or tamoxifen for postmenopausal, node (+) patients.
- Premenopausal women: recommend ovarian suppression (GnRH agonists sc qm for 2~3~5 years) or ablation + tamoxifen 10 mg bid/or AIs for 5 years; consider tamoxifen extended to 10 years.
- Options: Add abemaciclib x 2 years (monarchE[1]) for patients with 1. ≥ 4 positive ALN or 1-3 positive ALN plus histologic grade 3 and/or tumor ≥ 5 cm, 2. 1-3 positive ALN, Ki-67 ≥ 20% per central testing, not grade 3, tumor size < 5 cm

1. monarchE trail, SABCS 2020

Systemic Adjuvant Treatment - favorable histologies (Tubular, Mucinous, Papillary)

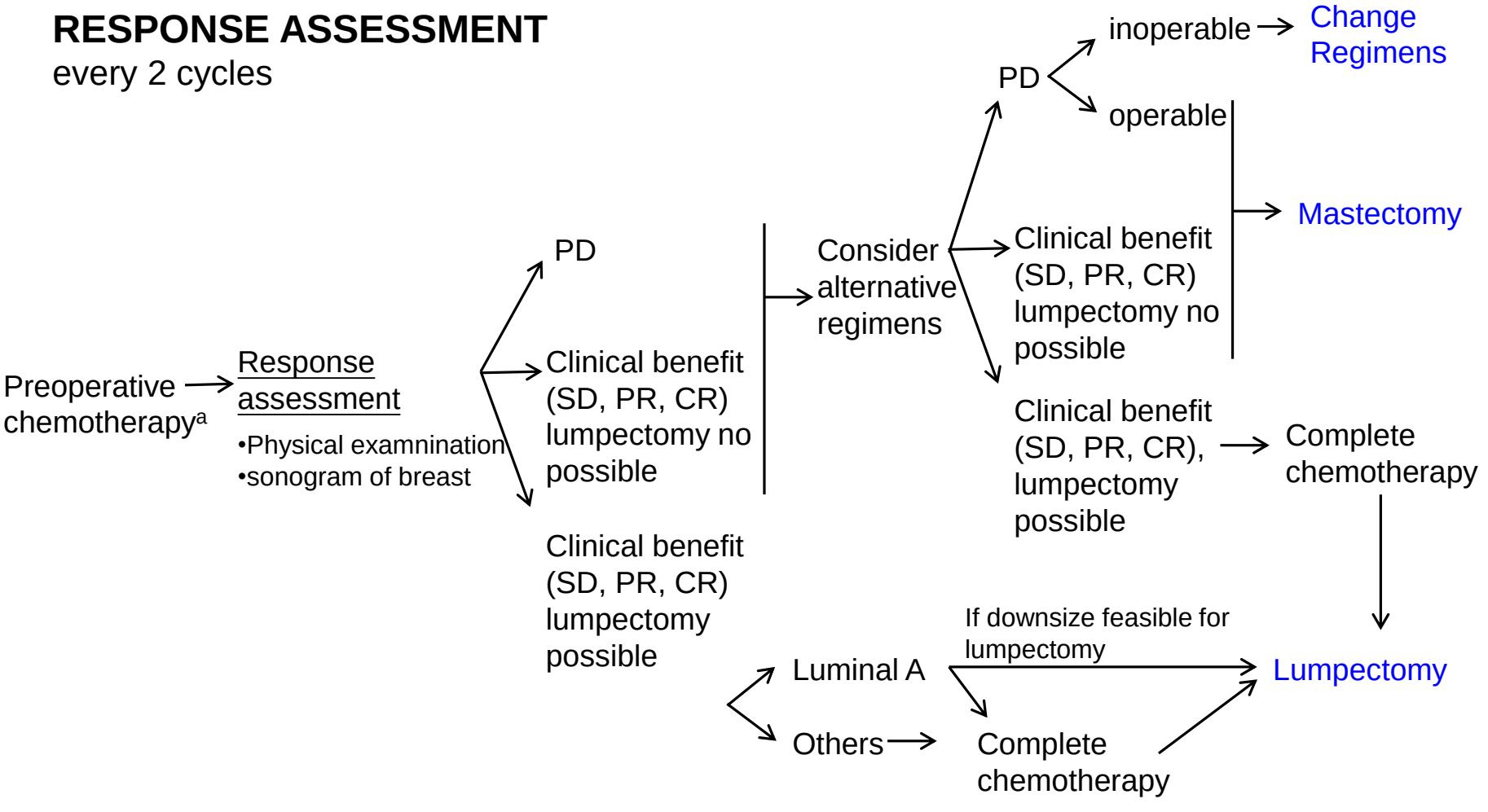


Preoperative systemic therapy guideline

WORKUP

- **History and physical exam**
- **CBC (including platelets), PT/APTT**
- **Liver and renal function tests and alkaline phosphatase**
- **Chest X-rays**
- **Diagnostic bilateral mammogram and breast ultrasound as necessary**
- **Pathology review if indicated, include:**
  - Estrogen/progesterone receptor (ER/PR) status
  - HER2 status
  - MIB-1 index
- **Staging surveillance**
  - Whole body bone scan
  - CT scan of chest
  - Abdominal ultrasound
- **Cardiac function (cardiac echography and/or MUGA)**
- **Hepatitis markers (HBsAg, anti-HBs,anti-HBc, anti-HCV Ab)**
- **Optional studies**
  - Tumor markers: CEA, CA-153
  - Breast MRI
  - PET/CT scan
  - Bone mineral density

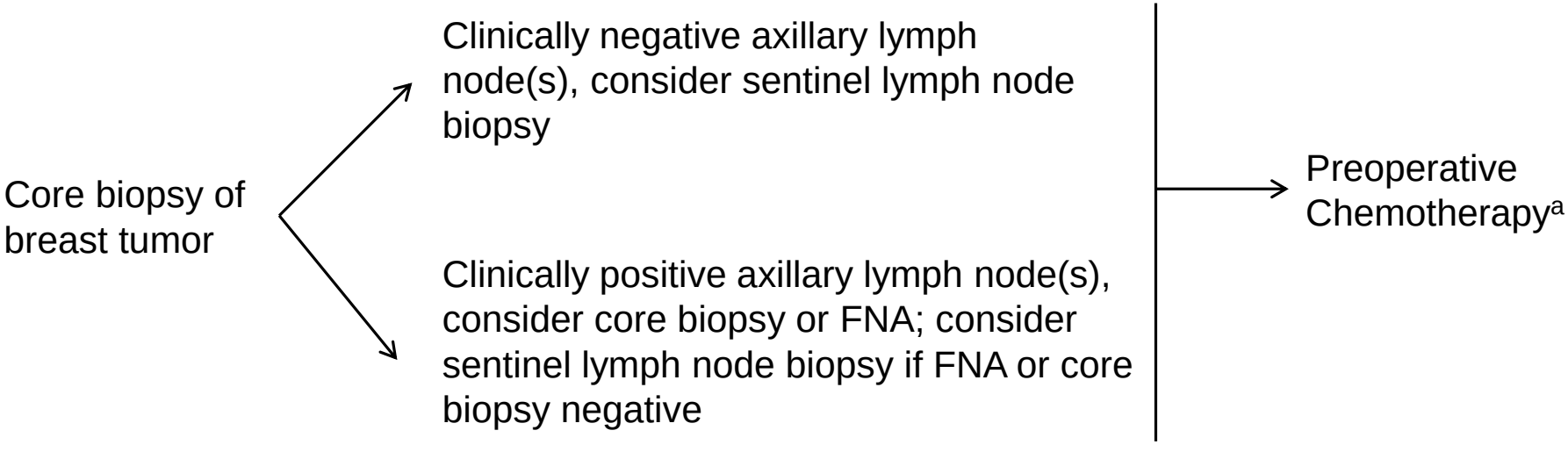
Preoperative systemic therapy guideline



[a] Regimens of preoperative chemotherapy refer to _____

Preoperative systemic therapy guideline

AXILLARY ASSESSMENT



[a] Consult gastroenterologist for lamivudine prophylaxis in HBV carrier before chemotherapy.

Neoadjuvant systemic therapy :

- Indications: (clinical stage) stage IIA (T2N0M0), stage IIB (T2N1M0; T3N0M0), stage IIIA (T3N1M0), and fulfills criteria for breast conserving surgery except for tumor size; stage IIIA (T3, N1, M0; T0, N2, M0; T1, N2, M0; T2, N2, M0; T3, N2, M0), stage IIIB(T4, N0, M0; T4, N1, M0; T4, N2, M0), stage IIIC(Any T, N3, M0)
- Clinical trials

Luminal A-like and Luminal B-like (HER2 negative)

- **Recommended regimens: taxane-based regimens q3w x 4 + E(90)C q3w x 4**
  - Taxane-based regimens: T-Carboplatin (docetaxel/carboplatin: 75/AUC 5-6 (if Ccr> 60 cc/min, carboplatin self-pay), T-CDDP (docetaxel/cisplatin 75/75), T (docetaxel 75). Weekly paclitaxel-carboplatin (80 qw x2-3, self-pay/ AUC 5-6. if Ccr> 60 cc/min, carboplatin self-pay), Weekly paclitaxel-cisplatin (80 qw x2-3/75), weekly paclitaxel (80 qw x 3).
- **Course-completion recommendation:**
  - Luminal A: Downsize large tumors for allowing more surgical options.
  - Luminal B-like (HER2 negative): If patients response continuously and are tolerable, complete total courses (8 cycles)

Luminal B-like (HER2 positive) and HER2 positive (non-luminal):

- **Recommended regimens: taxane-based regimens q3w x 4 + E(90)C q3w x 4 or docetaxel or paclitaxel/carboplatin or cisplatin x 6**
  - Taxane-based regimens: T-Carboplatin (docetaxel/carboplatin: 75/AUC 5-6 (if Ccr> 60 cc/min, carboplatin self-pay), T-CDDP (docetaxel/cisplatin 75/75), T (docetaxel 75). Weekly paclitaxel-carboplatin (80 qw x2-3, self-pay/ AUC 5-6. if Ccr> 60 cc/min, carboplatin self-pay), Weekly paclitaxel-cisplatin (80 qw x2-3/75), weekly paclitaxel (80 qw x 3).
- **Trastuzumab: standard dose from first cycle of chemotherapy, for 1 year**
- **Options:**

  Add pertuzumab (840 mg loading, then 420 mg q3w, self-pay) with trastuzumab, in 8 cycles of neoadjuvant chemotherapy, or continuous for 1 year if pCR obtained.
- **Course-completion' recommendation:** If patients response continuously and are tolerable, complete total courses (8 cycles)
- **If residual disease after preoperative therapy:** Ado-trastuzumab emtansine (T-DM1) (self-pay) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab ± pertuzumab to complete one year of therapy. (reference N Engl J Med. 2019 Feb 14;380(7):617-628.)

Triple Negative (Ductal)

- **Recommended regimens: taxane-based regimens q3w x 4 + E(90)C q3w x 4**
  - Taxane-based regimens: T-Carboplatin (docetaxel/carboplatin: 75/AUC 5-6 (if Ccr> 60 cc/min, carboplatin self-pay), T-CDDP (docetaxel/cisplatin 75/75), TC (docetaxel/cyclophosphamide 75/600), T (docetaxel 75). Weekly paclitaxel-carboplatin (80 qw x2-3, self-pay/ AUC 5-6. if Ccr> 60 cc/min, carboplatin self-pay), Weekly paclitaxel-cisplatin (80 qw x2-3/75), weekly paclitaxel (80 qw x 3).
- **Option:**

  1. add bevacizumab (15mg/kg q3w, self-pay)

  2. add atezolizumab (840 mg q2w, or 1200 mg q3w, exclusively nab-paclitaxel for taxane, reference[1]: IMpassion 031) or pembrolizumab (200mg q3w, reference[2]: KeyNote 522)
- **Course-completion' recommendation:**

If patients response continuously and are tolerable, complete total courses (8 cycles)

- **If Residual disease (no pCR) after neoadjuvant chemotherapy:** capecitabine 2000-2500 mg/m2 on days 1 to 14, every 3 weeks for 6 or 8 cycles (self-pay). (reference N Engl J Med. 2017 Jun 1;376(22):2147-2159)

1. IMpassion 031, 2. KeyNote 522, Schmid P, et al. N Engl J Med. 2020;382:810-821.

Neoadjuvant endocrine therapy in ER+ patients

- **Neoadjuvant endocrine therapy also accepted, especially in old age (≥ 70), or in patients who deny chemotherapy.**
- **Recommend regimens:**
  - Premenopausal patients: goserelin sc qm + tamoxifen 10 mg bid or letrozole 2.5 mg qd ± CDK 4/6 inhibitors (self-pay)
  - Postmenopausal patients: letrozole 2.5 mg qd ± CDK 4/6 inhibitors (self-pay)
  - Therapeutic aim: Downsize large tumors for allowing more surgical options

Treatment of local recurrence disease

- **Initial treatment with mastectomy > Surgical resection (if possible)+ RT (if possible)>Consider systemic therapy**
- **Initial treatment with lumpectomy + RT > Mastectomy > Consider systemic therapy**

Treatment of metastatic breast cancer

- **ER/PR positive and bone/soft tissue only/or asymptomatic visceral: sequential endocrine therapy or chemotherapy**
- **ER/PR negative or symptomatic visceral or hormone refractory : chemotherapy**
  - HER2 positive: Trastuzumab (+pertuzumab in first line) + chemotherapy
  - HER2 negative: chemotherapy

Preferred systemic therapy regimens for recurrent or metastatic breast cancer: as NCCN guidelines

- **Preferred regimens**
  - Anthracyclines: doxorubicin, epirubicin, liposomal doxorubicin
  - Taxanes: paclitaxel, docetaxel, albumin-bound paclitaxel
  - Anti-metabolites: capecitabine, gemcitabine
  - Microtubule inhibitors: vinorelbine, eribulin
  - PARP inhibitors (options for patients with HER2-negative tumors and germline BRCA1/2 mutation): olaparib, talazoparib
  - Platinum (option for patients with triple-negative tumors and germline BRCA1/2 mutation): carboplatin, cisplatin
  - Atezolizumab (self-pay) + nab-paclitaxel (self-pay)(option for patients with PD-L1-positive TNBC, reference[1]: Impassion 130/131)
  - Pembrolizumab (self-pay) + chemotherapy (preferred paclitaxel or nab-paclitaxel (self-pay), reference[2]: KeyNote 355) (option for patients with PD-L1-positive TNBC)
  - Cyclophosphamide
  - Ixabepilone
  - Trastuzumab deruxtecan (T-DXd)(self-pay) for HER2 IHC 1+ or 2+/ISH negative[3].

1. Impassion 130/131 studies, ESMO 2020, Schmid, N Engl J Med 2018. 2. KeyNote 355 study, ASCO 2020. 3. DESTINY-Breast04 study ASCO 2022. NCCN 2022.

Preferred systemic therapy regimens for recurrent or metastatic breast cancer (cont'd)

- **Useful in certain circumstances**
  - AC (doxorubicin/cyclophosphamide)
  - EC (epirubicin/cyclophosphamide)
  - CMF (cyclophosphamide/methotrexate/fluorouracil)
  - Docetaxel/capecitabine
  - TG (paclitaxel/gemcitabine)
  - Gemcitabine/carboplatin
  - Paclitaxel (or other chemotherapy) /bevacizumab
  - Cisplatin or carboplatin /5-FU
  - Vinorelbine/capecitabine, IV or oral.
  - Vinorelbine/platinum

Preferred systemic therapy regimens for recurrent or metastatic breast cancer (cont'd)

- **Preferred first-line agents for HER2-positive disease:**
  - Pertuzumab + trastuzumab + docetaxel
  - Pertuzumab + trastuzumab + paclitaxel

- **Other recommended regimens:**
  - Trastuzumab deruxtecan (T-DXd) (self-pay)(preferred second line)[1]
  - Ado-trastuzumab emtansine (T-DM1)(preferred second line)
  - Trastuzumab + paclitaxeli ± carboplatin
  - Trastuzumab + docetaxel
  - Trastuzumab + vinorelbine
  - Trastuzumab + capecitabine
  - Lapatinib + capecitabine
  - Trastuzumab + lapatinib (without cytotoxic therapy)
  - Trastuzumab + eribulin
  - Trastuzumab + other agents

1. DESTINY-Breast03 study. Cortés J et al. N Engl J Med. 2022;386:1143-1154

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[j]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[k]	Pertuzumab + trastuzumab + docetaxel[m]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[m]	Preferred Regimen	2A
Second line[l]	Fam-trastuzumab deruxtecan-nxki[l,n,o]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[l]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[m,p]	Other Recommended Regimen[p]	1
	Trastuzumab + docetaxel or vinorelbine[m,q]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[m,q]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[m,q]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[m,q] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[m,q,r,s]	Other Recommended Regimen	2A
	Neratinib + capecitabine[q]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[q] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

Preferred systemic therapy regimens for recurrent or metastatic breast cancer (cont'd)

- **Preferred Agents with Bevacizumab: Paclitaxel**
- **Preferred regimen for use in combination with lapatinib (HER2+)**
  - Capecitabine
- **Other Active Agents**
  - Cisplatin
  - Carboplatin
  - Etoposide (po)
  - Vinblastine
  - Fluorouracil continuous infusion
  - For germline BRCA1/2 mutation: olaparib[1], talazoparib[2]

1. N Engl J Med 2017;377:523-533. 2. N Engl J Med 2018;379:753-763.

Preferred endocrine therapy for recurrent or metastatic breast cancer

- **Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guideline.**
- **POSTMENOPAUSAL PATIENTS**
  - Aromatase inhibitors + CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib)
  - Fulvestrant + CDK 4/6 inhibitors
  - Tamoxifen + CDK 4/6 inhibitors
  - Non-steroidal aromatase inhibitor (anastrozole, letrozole)
  - Steroidal aromatase inactivator (exemestane)
  - Exemestane + everolimus
  - For PIK3CA-mutated tumors: alpelisib + fulvestrant[1]
  - Fulvestrant
  - Tamoxifen or Toremifene
  - Megestrol acetate

1. N Engl J Med 2018;379:2108-2121.

Preferred endocrine therapy for recurrent or metastatic breast cancer

- **HER2-Positive and Postmenopausal**
  - Aromatase inhibitor ± trastuzumab
  - Aromatase inhibitor ± lapatinib
  - Aromatase inhibitor ± lapatinib + trastuzumab
  - Fulvestrant ± trastuzumab
  - Tamoxifen ± trastuzumab

Dose reduction for hepatic and renal dysfunction- intravenous I		
	Hepatic function	Renal function
Carboplatin	X	By AUC
Cisplatin	X	Ccr 30-60: -50%, Ccr <30: Omit
Cyclophosphamide	TB 3-5 or AST>180: -25%, TB>5:Omit	Ccr 10-50: -25% Ccr <10: -50%
Docetaxel	TB > 1.5 AST>60 or ALKP >2.5 UNL: Omit	X
Doxorubicin	TB 1.5-3: -50% TB 3.1-5: -75% TB >5: Omit	X
Doxorubicin Liposome	TB 1.5-3: -50% TB 3.1-5: -75% TB >5: Omit	X
Epirubicin[b]	TB 1.5-3 or AST 2-4 UNL:-50%, TB>3 or AST>4 UNL:-75%	N/A
Etoposide	TB 1.5-3,or AST 60-180:-50%, TB >3 or AST>180: Omit	Ccr 10-50: -25%, Ccr <10: -50%

X: No recommendation, N/A: Not available, UNL: Upper normal limit,
Caution: Use carefully, dose reduction is/may be necessary

Dose reduction for hepatic and renal dysfunction- intravenous II		
	Hepatic function	Renal function
5-FU	TB >5: Omit	X
Gemcitabine	X	X
Goserelin	X	X
Leucovorin	X	X
Methotrexate	TB 3.1-5 or AST>180: -25%, TB >5: Omit	Ccr 30-60: -50%, Ccr <30: Omit
Paclitaxel	TB >5 or AST>180: Omit	X
Vinorelbine	TB 2-3: -50% TB 3.1-5: -75% TB>5: Omit	X
Eribulin	Child-Pugh Class A: 1.1 mg/m^2 Child-Pugh Class B: 0.7 mg/m^2 Child-Pugh Class C: Omit	Ccr 15-49: 1.1 mg/m^2 Ccr < 15: Omit HD: 80%
Ixabepilone	Combine Xeloda TB > 1 or ALT/AST > 2.5 x ULN : Omit Monotherapy TB < 1.5 and ALT/AST < 10 x ULN: 32 mg/m^2 TB > 1.5-3 and ALT/AST=10 x ULN: initial 20 mg/m^2, Max dose=30 mg/m^2 TB > 3 and ALT/AST>10 x ULN: Omit	Crea > 1.5 x ULN: no data
X: No recommendation, N/A: Not available, UNL: Upper normal limit, Caution: Use carefully, dose reduction is/may be necessary		

Dose reduction for hepatic and renal dysfunction- per os		
	Hepatic function	Renal function
Capecitabine	X	Ccr 30-50: -25%, Ccr <30: Omit
Cyclophosphamide	TB 3-5 or AST>180: -25%, TB>5:Omit	Ccr 10-50: -25%, Ccr <10: -50%
Etoposide	TB 1.5-3,or AST 60-180:-50%, TB >3 or AST>180: Omit	Ccr 10-50: -25%, Ccr <10: -50%
Lapatinib	Caution	X
Leucovorin	X	X
Megestrol acetate	X	N/A
Methotrexate	TB 3.1-5 or AST>180: -25%, TB >5: Omit	Ccr 30-60: -50%, Ccr <30: Omit
Tamoxifen	X	N/A
Vinorelbine	TB 2-3: -50% TB 3.1-5: -75% TB>5: Omit	X

X: No recommendation, N/A: Not available, UNL: Upper normal limit,
Caution: Use carefully, dose reduction is/may be necessary

Summary of Guidelines Updates in RT vs 2021

Presented in RO Guideline Meeting on 2022/06/15

- **Lumpectomy changed to breast-conserving surgery (BCS)**
- **In Abbreviated Guidelines for post-BCS RT, for 1-3 positive axilla nodes, criteria modified for consistency with NCCN guideline.**
- **IORT is not listed nor discussed in the 2022 NCCN guideline and should be restricted to patients who meet the "suitable criteria" of 2016 ASTRO APBI consensus and 2020 ESTRO IORT Task Force/ACROP recommendations.**
- **References are updated.**

Abbreviated Guidelines For Post-Operative Radiotherapy

- **Post- breast conserving surgery (BCS)**
  - Usually indicated for all BCS cases,
  - 40-42.5Gy in15-16 fractions (**preferred for no regional nodal irradiation**) or 45-50.4Gy to whole breast in 1.8~2 Gy per fraction
  - Conventional fractionation may be preferred when treating breast cancer with rare histologies
  - With or without **10~16Gy** boost to the tumor bed in **2~2.5 Gy** per fraction
    A boost to the tumor bed is recommended in higher risk patients (age ≤ 50, age 51-70 with high grade, positive axillary nodes, lymphovascular invasion, or positive or close margins).
  - **Simultaneous integrated boost (SIB)** to CTV_H with fraction size up to 2.2 Gy to shorten RT treatment time by one week
  - **Optional** for patient age ≥ 70 with **T1**N0, hormone receptor positive disease of low to intermediate grade and adequate (**≥ 2mm**) surgical margin
  - For patients with 1-3 positive axillary nodes disease who
    (1) meet **ALL** ACOSOG Z0011 criteria (cT1-2N0M0, underwent lumpectomy with planned whole breast radiation, 1-2 positive SLN, negative margin, no preoperative chemotherapy), regional nodal irradiation (RNI) with or without intentional inclusion of axilla is at the discretion of radiation oncologist
    (2) do not meet ALL ACOSOG Z0011 criteria, inclusion of any portion of undissected axilla at risk
- **Post-mastectomy**
  - Indications:
    - pN2 or pN3 (≥ 4 positive nodes or positive IMN)
    - pT3 (>5cm) or pT4
    - Positive margins
    - Strongly recommended for pT2N1a, and pT1N1a with ENE (extranodal extension), pT1-2N1 with triple negative breast cancer, pT1-2N1 with 3 positive LNs
    - Optional for pT1N1 without ENE
    - Optional for pT1-2N0-1 with close margin < 1mm
  - 50-54Gy in 25-30 fractions (1.8~2Gy per fraction)
  - Optional focal boost for positive margins or residual tumor
- **Post neoadjuvant RT**
  - Indications for post-operative RT and target volume delineation are usually based on the maximal disease stage at diagnosis and pathology results after neoadjuvant chemotherapy.
- **Irradiation of Internal Mammary Node (IMN)**
  - If IMN are clinically or pathologically positive, RT should be given to the IMN, otherwise the treatment to

Principles of Radiation Therapy

- **Post-BCS Radiation Therapy**
  - **Hypofractionated whole breast irradiation (HF-WBI) is preferred for invasive breast cancer without covering reginal lymph nodes, and DCIS**
    - 45 Gy in 20 fractions or 40~42.5 Gy in 15~16 fractions for DCIS if margin ≥ 2mm
    - 40~42.5 Gy in 15~16 fractions for IDC if margin ≥ 2 mm
    - For age ≤50, or high grade, positive or margin < 2mm, tumor bed boost should be given after HF-WBI
  - **Simultaneous Integrated Boost (SIB) to CTV_H with fraction size up to 2.2 cGy could be used to shorten RT treatment time by one week**
    - 55 Gy & 45 Gy in 25 fractions to primary tumor surgical bed and whole breast, respectively,
      - For DCIS with margin < 2 mm
      - For IDC with margins **>** 1mm
    - 60.2 Gy & 50.4 Gy in 28 fractions to primary tumor surgical bed and whole breast, respectively, for IDC with margins ≤ 1 mm
  - **Accelerated Partial Breast Irradiation (APBI)**
    - **Brachytherapy (interstitial or intracavitary)**
    - **EBRT: 3DCRT or IMRT**
    - **Intra-Operative Radiation Therapy (IORT)**
- **Post-mastectomy Radiation Therapy**
- **Irradiation of IMN**

Post-BCS Radiotherapy

- **Surgical Margin Status**
  - Patients with a positive margin should generally undergo either a re-excision or a mastectomy to achieve a negative margin.
  - It may be reasonable to treat selected BCS cases with a microscopically focally positive margin in the absence of an extensive intraductal component. For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.
- **Clinical Target Volume (CTV)**
  - CTV_H: Tumor bed, marked by surgical clips or post-operative seroma, with optional 5~10mm margin
  - CTV_M:
    - N0 diseases: Whole Breast Only
    - N0i+: Whole Breast +/- Supraclavicular Fossa (including level III axillary fossa)
    - pN1: Whole Breast +/- Supraclavicular Fossa (including level III axillary fossa). Patients who meet **ALL ACOSOG Z0011** criteria (cT1-2N0M0, underwent lumpectomy with planned whole breast radiation, 1-2 positive SLN, negative margin, no preoperative chemotherapy), RNI is at the discretion of radiation oncologist; if not ALL criteria are met, inclusion of any portion of undissected axilla at risk
    - pN2 or more: Whole Breast and Supraclavicular Fossa (including level III axillary fossa)
  - See Internal Mammary Node Irradiation for the inclusion criteria of IMN in CTV
- **Planning Target Volume (PTV)**
  - Dual Respiration Phase CT Simulation or 4D CT Simulation
    - 5mm around ITV (Internal Target Volume) with flash out of skin in tangential fields
  - Conventional CT Simulation (If dual phase CT simulation is not feasible)
    - 1cm around CTV with flash out of skin in tangential field
- **Radiation Dose**
  - CTV_M:
    - 45-50.4Gy in 25-28 fractions (1.8~2Gy per fraction)
    - 40-42.5 Gy in 15-16 fractions
  - CTV_H:
    - Negative margin:
      10 Gy boost in 4-5 fractions
    - Focally positive margin
      14-16 Gy in 7-8 fractions or 12.5 Gy in 5 fractions
  - See Internal Mammary Node Irradiation for the dose to IMN
- **Radiation Technique**
  - CT Simulation with 3D-CRT/IMRT* treatment planning
    *Breath-hold or other measure should be used to reduce target motion during IMRT
  - Whole Breast Irradiation
    - 3D Split-beam tangential fields or IMRT*
  - Supraclavicular Irradiation
    - Anterior split-beam for junction matching of 3D split-beam tangential field, or IMRT*
  - Boost to CTV_H
    - 3D coplanar or non-coplanar boost
    - Appositional Electron Beam Boost
    - Brachytherapy Boost
    - Simultaneous Integrated Boost (SIB) with fraction size up to 220cGy could be used to shorten RT treatment time by one week
- **Timing of Radiation Therapy**

  Within 6 weeks after the BCS or after the last course of adjuvant chemotherapy

Post-mastectomy Radiotherapy

- **Indications**
  - pN2 or pN3 (≥ 4 positive nodes or positive IMN)
  - pT3 (>5cm) or pT4
  - Positive margins
  - Strongly recommended for pT2N1a, and pT1N1a with ENE (extranodal extension), pT1-2N1 with triple negative breast cancer, pT1-2N1 with 3 positive LNs
  - Optional for pT1N1 without ENE
  - Optional for pT1-2N0-1 with close margin < 1mm

- **Clinical Target Volume (CTV)**
  - CTV_H:
    - Chest Wall and Supraclavicular Fossa (Including level III axillary fossa) for most cases
    - Chest Wall only, optional for cases with pT3N0 or N0+positive margin
- **Planning Target Volume (PTV)**
  - Dual Respiration Phase CT Simulation or 4D CT Simulation
    - 5mm around ITV (Internal Target Volume) with flash out of skin in tangential fields
  - Convention CT Simulation (If dual phase CT simulation is not feasible)
    - 1cm around CTV with flash out of skin in tangential field

- **Radiation Dose**
  - CTV_H:
    - 50-54Gy in 25-30 fractions (1.8~2Gy per fraction)
    - Optional focal boost to scar
    - Focal boost if positive margins or residual tumor
  - See Internal Mammary Node Irradiation for the dose to IMN
- **Radiation Technique**
  - CT Simulation with 3D-CRT/IMRT* treatment planning
    *Breath-hold or other measure should be used to reduce target motion during IMRT
  - Chest Wall Irradiation
    - 3D Split-beam tangential fields or 3D appositional electron beam field or IMRT*
    - Optimal application of bolus material to achieve adequate skin dose
  - Supraclavicular Irradiation
    - Anterior split-beam for junction matching of 3D split-beam tangential field or IMRT*
- **Timing of Radiation Therapy**

  Within 6 weeks after the mastectomy or after the last course of adjuvant chemotherapy.

Irradiation of Internal Mammary Node (IMN)

- **If IMN are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes, otherwise the treatment to the IMN is at the discretion of the treating radiation oncologist.**
- **If IMN irradiation should be planned as part of the post-operative radiotherapy after lumpectomy or after mastectomy, the dose to the additional target volume of IMN depends the extent of surgery.**
- **Clinical Target Volume (CTV)**
  - CTV_H_IMN: GTV of residual IMN
  - CTV_M_IMN: Post IMN Resection CTV to the cranial of border of 4th rib
- **Planning Target Volume (PTV)**
  - Dual Respiration Phase CT Simulation or 4D CT Simulation
    - A 5mm around ITV (Internal Target Volume)
  - Convention CT Simulation (If dual phase CT simulation is not feasible)
    - 1cm around CTV with flash out of skin in tangential field
- **Radiation Dose**
  - CTV_H_IMN:
    60~70Gy in 30~35 fractions
  - CTV_M_IMN:
    45~50.4Gy in 25~28 fractions
- **Radiation Technique**
  - 3-D conformal radiation or IMRT*.

Accelerated Partial Breast Irradiation (APBI)

- **Per NCCN guideline 2022, APBI is encouraged to be performed in clinical trial.**

- **APBI could be considered in selected low-risk patients after lumpectomy, per the "suitable criteria" of the 2016 American Society for Radiation Oncology (ASTRO) consensus, if:**
  - Tumor size: Invasive ≤2cm; DCIS ≤ 2.5cm
  - ER+, preferably luminal A, age ≥50
  - Unifocal primary tumor
  - N0, no lymph node metastases
  - DCIS with Nottingham grade 1-2
  - No BRCA mutation (if tested)
  - Invasive cancer, without EIC and LCIS
  - Adequate surgical margin
    - Invasive≥2mm, DCIS≥3mm,

- **Clinical Target Volume (CTV)**
  - CTV_H: Tumor bed plus 1 cm margin.
- **Planning Target Volume (PTV)**
  - Dual respiration phase CT simulation or 4D CT simulation
    - A 5mm around ITV (Internal Target Volume) when using photon radiation
  - Convention CT Simulation (If dual phase CT simulation is not feasible)
    - 1cm around CTV with flash out of skin in tangential field
- **Radiation Dose**
  - CTV_H:
    - **34 Gy in 10 fractions** delivered twice per day with brachytherapy
    - **38.5 Gy in 10 fractions** delivered twice per day with photon radiation
- **Radiation Technique**
  - Brachytherapy or 3-D external beam conformal radiation or IMRT.
- **Timing of Radiation Therapy**

  Within 6 weeks after the BCS or after the last course of adjuvant chemotherapy.

Intra-Operative Radiation Therapy (IORT) in BCS

- IORT is an extreme form of APBI, and should be performed only as part of a prospective trial.
- If not trial eligible, per the "**suitable criteria**" of the consensus statement of the ASTRO, IORT should be reserved for patients with negative surgical margin and a low risk of recurrence, should be avoided in patients with **diagnosis of invasive lobular carcinoma, positive margin, EIC and/or LCIS.**
  - 14% of Target-A requiring additional post-Op EBRT
- One of the most important differences of IORT from APBI is that the permanent pathology report of BCS is not available, and hence there is chance that IORT is applied to unsuitable cases with false negative frozen report of positive margin and/or positive sentinel node.
- If permanent pathology report shows adverse features, additional local treatment, either surgery or further external beam RT, is indicated. The patient should be well informed of the increased complication associated in this circumstance.

- **IORT is not currently endorsed or discussed in NCCN 2022 Breast Cancer Treatment Guideline.**
  - Update results of TARGIT trial, the 5-year IBTR **3.3% in IORT vs. 1.3 % in WBI** (**p=0.042**)
- **Clinical Target Volume (CTV)**
  - Surface of surgical cavity.
- **Planning Target Volume (PTV)**
  - No PTV with IORT
- **Radiation Dose**
  - CTV_H:
    - 20Gy single fraction per TARGIT-A trial
- **Radiation Technique**
  - Brachytherapy with suitable radiation source
- **Timing of Radiation Therapy**

  During BCS with frozen section report confirming negative margin, negative sentinel node, and other criteria listed in "suitable criteria" of 2016 ASTRO APBI consensus statement.

References

- Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy forbreast cancer: 5-year results for local control and overall survival from theTARGIT-A randomised trial. Lancet. 2014;383(9917): 603-613. Available at: https://pubmed.ncbi.nlm.nih.gov/24224997/
- Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-1277. Available at: https://pubmed.ncbi.nlm.nih.gov/24225155/
- Correa C, Harris EE, Leonardi MC et al, Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol*. 2017;7:73–79. Available at: https://pubmed.ncbi.nlm.nih.gov/27866865/
- Smith BD, Arthur DW, Buchholz TA et al, Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74:987–1001. Available at: https://pubmed.ncbi.nlm.nih.gov/19545784/
- Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol*. 2018;8(3):145-152. Available at: https://pubmed.ncbi.nlm.nih.gov/29545124/
- National Comprehensive Cancer Network. Breast Cancer (Version 3, May 7, 2022). https://www.nccn.org/professionals/physician_gls/pdf/breast. pdf. Accessed June 20, 2020
- Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24:3381-3387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16801628.
- Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355:528-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10683002.
- Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015;16:47-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25500422.
- Moran MS, Zhao Y, Ma S, et al. Association of Radiotherapy Boost for Ductal Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy. JAMA Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28358936.
- Gilleard O, Goodman A, Cooper M, et al. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World J Surg Oncol 2008;6:61-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18564426.

- Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving SurgeryWith Whole-Breast Irradiation in Ductal Carcinoma in Situ. Pract Radiat Oncol 2016;6:287-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27538810.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa022152.
- Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22019144.
- Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.Available at: http://www.ncbi.nlm.nih.gov/pubmed/24516019.
- .
- Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21304082.
- Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303-1310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25439688.
- Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26:2085-2092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18285602.
- Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18355913.
- Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426-432; discussion 432-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20739842

REFERENCES FOR NEOADJUVANT/ADJUVANT CHEMOTHERAPY REGIMENS

- Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741. J Clin Oncol 2003;21:1431-1439.
- Jones S, Holmes F, O'Shaughnessey J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735. J Clin Oncol 2009;27:1177-1183.
- Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8:1483-1496.
- Martin, Pienkowski T, Mackey J, et al: Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:22.
- Buzdar AU, Kau SW, Smith TL, Hortobagyi GN. Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. Am J Clin Oncol 1989;12; 123-128.
- Assikis V, Buzdar A, Yang Y, et al: A phase III trial of sequential adjuvant chemotherapy for operable breast carcinoma: final analysis with 10-year follow-up. Cancer 2003;97:2716-23.
- Bull JM, Tormey DC, Li SH, et al: A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978;41:1649-57.
- Levine MN, Bramwell VH, Pritchard KI, et al: Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1998;16:2651-8.
- Goldhirsch A, Colleoni M, Coates AS, et al: Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 1998;9:489-93.
- von Minckwitz G1, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol. 2005;23(12):2676-85.
- Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in adjuvant treatment of breast cancer. N Engl J Med 2008;258:1663-1671.
- Piccart MJ, Di Leo A, Beauduin M, et al: Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103-3110.
- Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 001 trial. J Clin Oncol 2006; 24:5664-5671.

REFERENCES FOR NEOADJUVANT/ADJUVANT CHEMOTHERAPY REGIMENS

- **Martin M, Rodriguez-Lescure A, Ruiz A, et al: Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by paclitaxel for early breast cancer. J Natl Cancer Inst 2008;100:805-814.**
- **Romond EH, Perez EZ, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. N Engl J Med 2005;353:1673-1684.**
- **Dang C, Fornier M, Sugarman S, et al: The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/ amplified breast cancer. J Clin Oncol 2008;26(8):1216-22.**
- **Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-1283.**
- **18Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-2284.**
- **Jones SE, Collea R, Paul D, et al. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a singlegroup, open-label, phase 2 study. Lancet Oncol 2013;14:1121-8.**
- **Tolaney S, Barry W, Dang C, et al. Adjuvant paclitaxel and trastuzumab for node-negative HER2-positive breast cancer. N Engl J Med 2015;372:134-141.**
- **Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2- positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.**

REFERENCES FOR DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

- Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999;17:2341- 2354.
- Gasparini G, Dal Fior S, Panizzoni GA, et al. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. Am J Clin Oncol 1991;14:38-44.
- O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15:440-449.
- Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 1995;13:2575-2581.
- Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001;19:4216-4223.
- Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;23:2155-2161.
- Seidman AD. Gemcitabine as single-agent therapy in the management of advanced breast cancer. Oncology (Williston Park) 2001;15:11-14.
- Zelek L, Barthier S, Riofrio M, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer 2001;92:2267-2272.
- Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914-923.
- Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. J Chemother 2010;22(3):201-4.
- Isakoff, SJ, Goss PE, et al. (2011). TBCRC009: A multicenter phase II study of cisplatin or carboplatin for metastatic triple-negative breast cancer and evaluation of p63/p73 as a biomarker of response [abstract]. J Clin Oncol 29(15_suppl): Abstract 1025.
- Burris HA, 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials. Semin Oncol 1999;26:1-6.

REFERENCES FOR DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

- Harvey V, Mouridsen H, Semiglazov V, et al: Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol 2006;24(31):4963-70.
- Rivera E, Mejia JA, Arun BJ, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 2008 Apr 1;112(7):1455-61.
- Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794-7803.
- Gradishar W, Dimitry K, Sergey C, et al: Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 2009;27(22):3611-9.
- Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28(7):1145-53.
- Bastholt L, Dalmark M, Gjedde SB, et al. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. J Clin Oncol 1996;14:1146-1155.
- Perez E, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol 2007;25(23):3407-14.
- Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978;41:1649-1657.
- Hortobagyi GN, Gutterman JU, Blumenschein GR, et al: Combination chemoimmunotherapy of metastatic breast cancer with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG. Cancer 1979;43:1225-33.
- Ackland SP, Anton A, Breitbach GP, et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. J Clin Oncol 2001;19:943-953.
- Nabholtz JM, Falkson C, Campos D, et al: Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003; 21(6): 968-75.

REFERENCES FOR DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

- Langley RE, Carmichel J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclphosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom Cancer Research Institute. J Clin Oncol 2005;23:8322-8330.
- Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-410.
- Mavroudis D, Papakotoulas P, Ardavanis A, et al. Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. Ann Oncol 21:48(2010).
- Albain KS, Nag S, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol 2008;26(24):3950-7.
- O'Shaughnessy J, Schwartzberg LS, Danso MA, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). [abstract]. J Clin Oncol 2011;29 (Suppl_15):Abstract 1007.
- Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-2676.
- Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-119.
- Datko F, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer [abstract]. Cancer Research 2012;72:Abstract P5-18-20.
- Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786-2792.
- Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol 2003;21:3965-3971.

REFERENCES FOR DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

- Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. Clin Breast Cancer 2005;6:425-432.
- Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792.
- Seidman A, Berry DA, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008;26:1642-1649.
- Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23:4265-4274.
- Esteva FJ, Valero V, Booser D, et al. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:1800-1808.
- Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965-972.
- Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol 2011;29:264-271.
- von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006.
- Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2- overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-2648.
- Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer [supplementary appendix available online]. N Engl J Med 2012;367:1783-1791.

REFERENCES FOR DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

- **Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-2743.**
- **Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853-3858.**
- **Blackwell KL, Burstein H, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28(7):1124-30**

Reference: PATHOLOGY AND STAGING

- WHO Classification of Tumours Editorial Board: WHO Classification of Tumours of the Breast, 5th eds. IARC: Lyon 2019
- Rosen PP. Tumor emboli in intramammary lymphatics in breast carcinoma: pathologic criteria for diagnosis and clinical significance. Pathol Annu. 1983;18 Pt 2:215-32.
- Consensus conference on the classification of ductal carcinoma in situ. Hum Pathol. 1997; 28(11):1221-5.
- Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med 2010;134:907-22
- Wolff AC, Hammond MEH, Allison KH et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update.. Arch Pathol Lab Med 2018; 142:1364-1382.
- Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.

REFERENCE: Treatment Approach

- **Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med 2002;137:678-687.**
- **Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002;25:235-237.**

REFERENCE: Pure Noninvasive Carcinomas (Stage 0)

- Rosai J. Borderline epithelial lesions of the breast. Am J Surg Pathol 1991;15:209-221.
- Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. Am J Surg Pathol 1992;16:1133-1143.
- Renshaw AA, Derhagopian RP, Martinez P, Gould EW. Lobular neoplasia in breast core needle biopsy specimens is associated with a low risk of ductal carcinoma in situ or invasive carcinoma on subsequent excision. Am J Clin Pathol 2006;126:310-313.
- Nagi CS, O'Donnell JE, Tismenetsky M, et al. Lobular neoplasia on core needle biopsy does not require excision. Cancer 2008;112:2152-2158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18348299.
- Hwang H, Barke LD, Mendelson EB, Susnik B. Atypical lobular hyperplasia and classic lobular carcinoma in situ in core biopsy specimens: routine excision is not necessary. Mod Pathol 2008;21:1208-1216.
- Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. Am J Surg Pathol 2005;29:534-543.
- Karabakhtsian RG, Johnson R, Sumkin J, Dabbs DJ. The clinical significance of lobular neoplasia on breast core biopsy. Am J Surg Pathol 2007;31:717-723.
- O'Neil M, Madan R, Tawfik OW, et al. Lobular carcinoma in situ/atypical lobular hyperplasia on breast needle biopsies: does it warrant surgical excisional biopsy? A study of 27 cases. Ann Diagn Pathol 2010;14:251-255.
- Foster MC, Helvie MA, Gregory NE, et al. Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional biopsy necessary? Radiology 2004;231:813-819.
- Hussain M, Cunnick GH. Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast--a review. Eur J Surg Oncol 2011;37:279-289.
- Rendi MH, Dintzis SM, Lehman CD, et al. Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. Ann Surg Oncol 2012;19:914-921.
- Anderson BO, Calhoun KE, Rosen EL. Evolving concepts in the management of lobular neoplasia. J Natl Compr Canc Netw 2006;4:511-522.
- Kerlikowske K, Molinaro AM, Gauthier ML, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. J Natl Cancer Inst 2010;102:627-637.
- Stackievicz R, Paran H, Bernheim J, et al. Prognostic significance of HER-2/neu expression in patients with ductal carcinoma in situ. Isr Med Assoc J 2010;12:290-295.

REFERENCE: Pure Noninvasive Carcinomas (Stage 0)

- Zhou W, Jirstrom K, Johansson C, et al. Long-term survival of women with basal-like ductal carcinoma in situ of the breast: a population-based cohort study. BMC Cancer 2010;10:653.
- Lari SA, Kuerer HM. Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. J Cancer 2011;2:232-261.
- Kuhl CK, Schrading S, Bieling HB, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet 2007;370:485-492.
- Kowalchik KV, Vallow LA, McDonough M, et al. The role of preoperative bilateral breast magnetic resonance imaging in patient
- selection for partial breast irradiation in ductal carcinoma in situ. Int J Surg Oncol 2012;2012:206342.
- Brennan ME, Turner RM, Ciatto S, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. Radiology 2011;260:119-128.
- Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24:3381-3387.
- Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol
- 1998;16:441-452.
- Vargas C, Kestin L, Go N, et al. Factors associated with local recurrence and cause-specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy. Int J Radiat Oncol Biol Phys 2005;63:1514-1521.
- Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS:Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 2006;45:536-543.
- Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 2003;362:95-9102.
- Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breastconserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355:528-533.

REFERENCE: Pure Noninvasive Carcinomas (Stage 0)

- Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12:21-29.
- Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103:478-488.
- Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol 2008;26:1247-1252.
- Di Saverio S, Catena F, Santini D, et al. 259 Patients with DCIS of the breast applying USC/Van Nuys prognostic index: a retrospective review with long term follow up. Breast Cancer Res Treat 2008;109:405-416.
- Gilleard O, Goodman A, Cooper M, et al. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World J Surg Oncol 2008;6:61-61.
- Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77:2267-2274.
- Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999;340:1455-1461.
- Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:5319-5324.
- Wong P, Lambert C, Agnihotram RV, et al. Ductal carcinoma in situthe influence of the radiotherapy boost on local control. Int J Radiat Oncol Biol Phys 2011.
- Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast--a systematic review of the randomised trials. Breast 2009;18:143-149.
- MacDonald HR, Silverstein MJ, Mabry H, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. Am J Surg 2005;190:521-525.
- Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. J Clin Oncol 2009;27:1615-1620.
- Groot G, Rees H, Pahwa P, et al. Predicting local recurrence following breast-conserving therapy for early stage breast cancer: the significance of a narrow (</= 2 mm) surgical resection margin. J Surg Oncol 2011;103:212-216.
- Waddell BE, Stomper PC, DeFazio JL, et al. Postexcision mammography is indicated after resection of ductal carcinoma-in-situ of the breast. Ann Surg Oncol 2000;7:665-668.
- Julian TB, Land SR, Fourchotte V, et al. Is sentinel node biopsy necessary in conservatively treated DCIS? Ann Surg Oncol 2007;14:2202-2208.

REFERENCE: Pure Noninvasive Carcinomas (Stage 0)

- **Cody HS, Van Zee KJ. Point: sentinel lymph node biopsy is indicated for patients with DCIS. J Natl Compr Canc Netw 2003;1:199-206.**
- **Edge SB, Sheldon DG. Counterpoint: sentinel lymph node biopsy is not indicated for ductal carcinoma in situ. J Natl Compr Canc Netw 2003;1:207-212.**
- **Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703-7720.**
- **Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst2005;97:1652-1662.**
- **Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-1388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9747868.**
- **Tan-Chiu E, Wang J, Costantino JP, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. J Natl Cancer Inst 2003;95:302-307.**
- **Allred DC, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from the NSABP Protocol B-24 [abstract]. Breast Cancer Res Treat 2002;76(Suppl 1):Abstract A30.**

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Esserman L. Integration of Imaging in the Management of Breast Cancer. J Clin Oncol 2005;23:1601-1602.
- Gundry KR. The application of breast MRI in staging and screening for breast cancer. Oncology (Williston Park) 2005;19:159-169.
- Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248-3258.
- Miller BT, Abbott AM, Tuttle TM. The influence of preoperative MRI on breast cancer treatment. Ann Surg Oncol 2012;19:536-540.
- Peters NH, van Esser S, van den Bosch MA, et al. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. Eur J Cancer 2011;47:879-886.
- Turnbull LW, Brown SR, Olivier C, et al. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). Health Technol Assess 2010;14:1-182.
- Fischer U, Zachariae O, Baum F, et al. The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol 2004;14:1725-1731.
- Solin LJ, Orel SG, Hwang W-T, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation
- treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol 2008;26:386-391.
- Baucom DH, Porter LS, Kirby JS, et al. Psychosocial issues confronting young women with breast cancer. Breast Dis 2005;23:103-113.
- Dunn J, Steginga SK. Young women's experience of breast cancer:defining young and identifying concerns. Psychooncology 2000;9:137-146.
- Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol 2003;21:4184-4193.
- Gorman JR, Bailey S, Pierce JP, Su HI. How do you feel about fertility and parenthood? The voices of young female cancer survivors. Cancer Surviv 2012;6:200-209.
- Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst 2012;104:386-405.
- Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? Breast J 2010;16:404-411.
- Cruz MR, Prestes JC, Gimenes DL, Fanelli MF. Fertility preservation in women with breast cancer undergoing adjuvant chemotherapy: a systematic review. Fertil Steril 2010;94:138-143.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Dunn L, Fox KR. Techniques for fertility preservation in patients with breast cancer. Curr Opin Obstet Gynecol 2009;21:68-73.
- Oktem O, Oktay K. Fertility preservation for breast cancer patients.Semin Reprod Med 2009;27:486-492.
- Redig AJ, Brannigan R, Stryker SJ, et al. Incorporating fertility preservation into the care of young oncology patients. Cancer 2011;117:4-10.
- Lee S, Ozkavukcu S, Heytens E, et al. Value of early referral to fertility preservation in young women with breast cancer. J Clin Oncol 2010;28:4683-4686.
- Lobo RA. Potential options for preservation of fertility in women. N Engl J Med 2005;353:64-73.
- Sukumvanich P, Case LD, Van Zee K, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. Cancer 2010;116:3102-3111.
- Peate M, Meiser B, Friedlander M, et al. It's now or never: fertilityrelated knowledge, decision-making preferences, and treatment intentions in young women with breast cancer--an Australian fertility decision aid collaborative group study. J Clin Oncol
- Baseline staging tests in primary breast cancer: Practice guideline report # 1-14: Members of the Breast Cancer Disease Site
- Puglisi F, Follador A, Minisini AM, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol 2005;16:263-266.
- Kumar R, Chauhan A, Zhuang H, et al. Clinicopathologic factors associated with false negative FDG-PET in primary breast cancer. Breast Cancer Res Treat 2006;98:267-274.
- Podoloff DA, Advani RH, Allred C, et al. NCCN task force report:positron emission tomography (PET)/computed tomography (CT)scanning in cancer.J Natl Compr Canc Netw 2007;5 Suppl 1:1-1.
- Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. Radiographics 2007;27 Suppl 1:S215-229.
- Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. J Clin Oncol 2004;22:277-285.
- Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol 1996;14:1558-1564.
- Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.Lancet 2005;366:2087-2106.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.N Engl J Med 2002;347:1233-1241.
- Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-1232.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P,et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-1716.
- Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol
- 2014;32:1507-1515.
- Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys 1989;17:719-725.
- Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast
- cancer: risk factors and impact on distant metastases. Cancer 2006;106:35-41.
- Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breastconserving therapy. Breast Cancer Res Treat 2007;101:51-57.
- Golshan M, Miron A, Nixon AJ, et al. The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy. Am J Surg 2006;192:58-62.
- Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breastconserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer 2004;100:688-693.
- Recht A. Contralateral prophylactic mastectomy: caveat emptor. J Clin Oncol 2009;27:1347-1349.
- Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst 2010;102:401-409.
- Jatoi I, Parsons HM. Contralateral prophylactic mastectomy and its association with reduced mortality: evidence for selection bias. Breast Cancer Res Treat 2014;148:389-396.
- Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. J Natl Cancer Inst 2014;106.
- Fayanju OM, Stoll CR, Fowler S, et al. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. Ann Surg 2014;260:1000-1010.
- Bass SS, Lyman GH, McCann CR, et al. Lymphatic mapping and sentinel lymph node biopsy. Breast J 1999;5:288-295.
- Cox CE. Lymphatic mapping in breast cancer: combination technique. Ann Surg Oncol 2001;8:67S-70S.
- Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001;67:513-519.
- Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer--a multicenter validation study. N Engl J Med 1998;339:941-946.
- Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survivalfindings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11:927-933.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Kuehn T, Vogl FD, Helms G, et al. Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospective German multiinstitutional trial. Eur J Surg Oncol 2004;30:252-259.
- McMasters KM, Giuliano AE, Ross MI, et al. Sentinel-lymph-node biopsy for breast cancer--not yet the standard of care. N Engl J Med 1998;339:990-995.
- O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J Am Coll Surg 1998;186:423-427.
- Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.N Engl J Med 2003;349:546-553.
- Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609.
- Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001;193:593-600.
- Dupont E, Cox C, Shivers S, et al. Learning curves and breast cancer lymphatic mapping: institutional volume index. J Surg Res2001;97:92-96.
- Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA 2011;306:385-393.
- Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am J Surg 2005;190:543-550.
- Houvenaeghel G, Nos C, Giard S, et al. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. Eur J Surg Oncol 2009;35:690-695.
- Katz A, Smith BL, Golshan M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer. J Clin Oncol 2008;26:2093-2098.
- Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer 2008;8:66-66.
- Scow JS, Degnim AC, Hoskin TL, et al. Assessment of the performance of the Stanford Online Calculator for the prediction of
- nonsentinel lymph node metastasis in sentinel lymph node-positive breast cancer patients. Cancer 2009;115:4064-4070.
- van la Parra RFD, Ernst MF, Bevilacqua JLB, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. Ann Surg Oncol 2009;16:1128-1135.
- Werkoff G, Lambaudie E, Fondrinier E, et al. Prospective multicenter comparison of models to predict four or more involved axillary lymph nodes in patients with breast cancer with one to three metastatic sentinel lymph nodes. J Clin Oncol 2009;27:5707-5712.
- Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426-432; discussion 432-423.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-575.
- Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415-1418.
- Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 1992;69:2496-2501.
- Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;312:674-681.
- Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. Radiother Oncol 2007;82:265-271.
- Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001;345:1378-1387.
- Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26:2085-2092.
- Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. J Clin Oncol 2013;31:4488-4495.
- Mulliez T, Veldeman L, van Greveling A, et al. Hypofractionated whole breast irradiation for patients with large breasts: a randomized trial comparing prone and supine positions. Radiother Oncol 2013;108:203-208.
- Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098-1107.
- Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331-341.
- Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006;7:467-471.
- Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-520.
- Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086-1094.
- Werkhoven E, Hart G, Tinteren H, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. Radiother Oncol 2011;100:101-107.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Whelan TJ, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer [abstract]. J Clin Oncol 2011;29 (18_suppl):LBA1003.
- McCormick B. Partial-breast radiation for early staged breast cancers: hypothesis, existing data, and a planned phase III trial. J Natl Compr Canc Netw 2005;3:301-307.
- Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74:987-1001.
- Shaitelman SF, Vicini FA, Beitsch P, et al. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. Cancer 2010;116:4677-4685.
- Vicini F, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology Consensus Panel Guidelines on the Use of Accelerated Partial Breast Irradiation. Int J Radiat Oncol Biol Phys 2010.
- Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer:
- updated results of a prospective randomized trial. J Clin Oncol 2005;23:1934-1940.
- Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334:1356-1361.
- Jones HA, Antonini N, Hart AA, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. J Clin Oncol 2009;27:4939-4947.
- Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971-977.
- Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382-2387.
- Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004;351:963-970.
- Hellman S. Stopping metastases at their source. N Engl J Med 1997;337:996-997.
- Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949-955.
- Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641-1648.
- Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial.J Natl Cancer Inst 2005;97:116-126.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy:clinical practice guidelines of the American Society of Clinical Oncology.J Clin Oncol 2001;19:1539-1569. Available at:http://www.ncbi.nlm.nih.gov/pubmed/11230499.
- Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004;22:4691-4699.
- McGuire SE, Gonzalez-Angulo AM, Huang EH, et al.Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2007;68:1004-1009.
- Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007;82:247-253.
- Early Breast Cancer Trialists' Collaborative G, McGale P, Taylor C,et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.Lancet 2014;383:2127-2135.
- Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006;24:2268-2275.
- Jagsi R, Raad RA, Goldberg S, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. Int J Radiat Oncol Biol Phys 2005;62:1035-1039.
- Abdulkarim BS, Cuartero J, Hanson J, et al. Increased risk of locoregional recurrence for women With T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. Journal of Clinical Oncology 2011;29:2852-2858.
- Liu AS, Kao HK, Reish RG, et al. Postoperative complications in prosthesis-based breast reconstruction using acellular dermal matrix.Plast Reconstr Surg 2011;127:1755-1762.
- McCarthy CM, Mehrara BJ, Riedel E, et al. Predicting complications following expander/implant breast reconstruction: an outcomes analysis based on preoperative clinical risk. Plast Reconstr Surg 2008;121:1886-1892.
- Cowen D, Gross E, Rouannet P, et al. Immediate post-mastectomy breast reconstruction followed by radiotherapy: risk factors for complications. Breast Cancer Res Treat 2010;121:627-634.
- Woerdeman LA, Hage JJ, Hofland MM, Rutgers EJ. A prospective assessment of surgical risk factors in 400 cases of skin-sparing mastectomy and immediate breast reconstruction with implants to establish selection criteria. Plast Reconstr Surg 2007;119:455-463.
- Antony AK, McCarthy CM, Cordeiro PG, et al. Acellular human dermis implantation in 153 immediate two-stage tissue expander breast reconstructions: determining the incidence and significant predictors of complications. Plast Reconstr Surg 2010;125:1606-1614.
- Ahmed S, Snelling A, Bains M, Whitworth IH. Breast reconstruction. BMJ 2005;330:943-948.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Edlich RF, Winters KL, Faulkner BC, et al. Advances in breast reconstruction after mastectomy. J Long Term Eff Med Implants 2005;15:197-207.
- Pennington DG. Breast reconstruction after mastectomy: current state of the art. ANZ J Surg 2005;75:454-458.
- Chang DW. Breast Reconstruction with Microvascular MS-TRAM and DIEP Flaps. Arch Plast Surg 2012;39:3-10.
- Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. Plast Reconstr Surg 2009;124:395-408.
- Tran NV, Chang DW, Gupta A, et al. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001;108:78-82.
- Mehta VK, Goffinet D. Postmastectomy radiation therapy after TRAM flap breast reconstruction. Breast J 2004;10:118-122.
- Berry T, Brooks S, Sydow N, et al. Complication rates of radiation on tissue expander and autologous tissue breast reconstruction. Ann Surg Oncol 2010;17 Suppl 3:202-210.
- Francis SH, Ruberg RL, Stevenson KB, et al. Independent risk factors for infection in tissue expander breast reconstruction.Plast Reconstr Surg 2009;124:1790-1796.
- Colwell AS, Damjanovic B, Zahedi B, et al. Retrospective review of 331 consecutive immediate single-stage implant reconstructions with acellular dermal matrix: indications, complications, trends, and costs.Plast Reconstr Surg 2011;128:1170-1178.
- Garcia-Etienne CA, Cody Iii HS, Disa JJ, et al. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. Breast J 2009;15:440-449.
- Petit JY, Veronesi U, Orecchia R, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). Breast Cancer Res Treat 2009;117:333-338.
- Yueh JH, Houlihan MJ, Slavin SA, et al. Nipple-sparing mastectomy: evaluation of patient satisfaction, aesthetic results, and sensation. Ann Plast Surg 2009;62:586-590.
- Chung AP, Sacchini V. Nipple-sparing mastectomy: Where are we now? Surg Oncol 2008;17:261-266.
- Gerber B, Krause A, Dieterich M, et al. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg 2009;249:461-468.
- Mallon P, Feron JG, Couturaud B, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. Plast Reconstr Surg 2013;131:969-984.
- Piper M, Peled AW, Foster RD, et al. Total Skin-Sparing Mastectomy: A Systematic Review of Oncologic Outcomes and Postoperative Complications. Ann Plast Surg 2013.

REFERENCE: Stage I, IIA, IIB, or T3N1M0

- Toth BA, Forley BG, Calabria R. Retrospective study of the skinsparing mastectomy in breast reconstruction. Plast Reconstr Surg 1999;104:77-84.
- Carlson GW, Styblo TM, Lyles RH, et al. The use of skin sparing mastectomy in the treatment of breast cancer: The Emory experience.Surg Oncol 2003;12:265-269.
- Downes KJ, Glatt BS, Kanchwala SK, et al. Skin-sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high-risk breast carcinoma. Cancer 2005;103:906-913.
- Foster RD, Esserman LJ, Anthony JP, et al. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. Ann Surg Oncol 2002;9:462-466.
- Medina-Franco H, Vasconez LO, Fix RJ, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. Ann Surg 2002;235:814-819.
- Newman LA, Kuerer HM, Hunt KK, et al. Presentation, treatment, and outcome of local recurrence afterskin-sparing mastectomy and immediate breast reconstruction. Ann Surg Oncol 1998;5:620-626.
- Clough KB, Kaufman GJ, Nos C, et al. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol 2010;17:1375-1391.
- Anderson BO, Masetti R, Silverstein MJ. Oncoplastic approaches to partial mastectomy: an overview of volume-displacement techniques.Lancet Oncol 2005;6:145-157.
- Huemer GM, Schrenk P, Moser F, et al. Oncoplastic techniques allow breast-conserving treatment in centrally located breast cancers. Plast Reconstr Surg 2007;120:390-398.
- Kaur N, Petit J-Y, Rietjens M, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer.Ann Surg Oncol 2005;12:539-545.

REFERENCE: Systemic Adjuvant Therapy

- Early Breast Cancer Trialists' Collaborative G, Peto R, Davies C, et al.Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432-444.
- Loprinzi CL, Thome SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. J Clin Oncol 2001;19:972-979.
- Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19:980-991.
- Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer.J Clin Oncol 2005;23:2716-2725.
- Loprinzi CL, Ravdin PM. Decision-making for patients with resectable breast cancer: individualized decisions for and by patients and their physicians. J Natl Compr Canc Netw 2003;1:189-196. Cooke T, Reeves J, Lanigan A, Stanton P. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol 2001;12 Suppl 1:23-28.
- Paik S, Bryant J, Park C, et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst 1998;90:1361-1370.
- Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst 2000;92:1991-1998.
- Piccart MJ, Di Leo A, Hamilton A. HER2. a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer 2000;36:1755-1761.
- Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103-2111.
- Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 1998;90:1346-1360.
- Dressler LG, Berry DA, Broadwater G, et al. Comparison of HER2 status by fluorescence in situ hybridization and immunohistochemistry to predict benefit from dose escalation of adjuvant doxorubicin-based therapy in node-positive breast cancer patients. J Clin Oncol 2005;23:4287-4297.
- Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.N Engl J Med 2006;354:809-820.
- Piccart-Gebhart M, Procter M, Leyland-Jones B, et al.Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-1672.
- Goldhirsch A, Piccart-Gebhart M, Procter M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. Cancer Research 2012;72:S5-2.
- Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-1684.
- Romond E, Suman V, Jeong J-H, et al. Trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer: Final planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831.Cancer Research 2012;72:S5-5.

REFERENCE: Systemic Adjuvant Therapy

- Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-1283.
- Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-2648.
- Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792.
- Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-726.
- Jeffrey SS, Lonning PE, Hillner BE. Genomics-based prognosis and therapeutic prediction in breast cancer. J Natl Compr Canc Netw 2005;3:291-300.
- Perou CM, Jeffrey SS, van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci U S A 1999;96:9212-9217.
- Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-10874. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418-8423.
- Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-2826.
- Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol 2010;28:1829-1834.
- Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28:1677-1683.
- Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010;11:55-65.
- Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726-3734.
- Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer:results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat2011;127:133-142.
- Glas AM, Floore A, Delahaye LJMJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics 2006;7:278-278.

REFERENCE: Systemic Adjuvant Therapy

- van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009.
- van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530-536.
- Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer.Breast Cancer Res Treat 2010;120:655-661.
- Kunz G. Use of a genomic test (MammaPrint) in daily clinical practice to assist in risk stratification of young breast cancer patients.Arch Gynecol Obstet 2011;283:597-602.
- Ishitobi M, Goranova TE, Komoike Y, et al. Clinical utility of the 70-gene MammaPrint profile in a Japanese population. Jpn J Clin Oncol 2010;40:508-512.
- Mook S, Knauer M, Bueno-de-Mesquita JM, et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. Ann Surg Oncol 2010;17:1406-1413.
- Drukker CA, Bueno-de-Mesquita JM, Retel VP, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int J Cancer 2013;133:929-936..
- Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol 2013;31:2783-2790.
- Hormone therapy with or without combination chemotherapy in treating women who have undergone surgery for node-negative breast cancer (The TAILORx Trial). Clinical Trial ID: NCT00310180.
- A phase III, randomized clinical trial of standard adjuvant endocrine therapy +/-chemotherapy in patients with 1-3 positive nodes,hormone receptor-positive and HER2-negative breast cancer with recurence score (RS) of 25 or less. RXPONDER: A clinical trial RX for positive node, endocrine responsive breast cancer. Clincial Trial ID NCT01272037.
- MINDACT (Microarray In Node-Negative and 1 to 3 positive lymph node disease may avoid chemotherapy): A prospective, randomized study comparing the 70-Gene signature with the common clinicalpathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes. Clinical Trial ID:
- NCT00433589.
- Swain SM, Wilson JW, Mamounas EP, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96:516-523.
- Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with nodepositive breast cancer. JAMA 2006;295:1658-1667.
- Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrineresponsive,node-positive breast cancer: a phase 3, open-label,randomised controlled trial. Lancet 2009;374:2055-2063.
- Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451-1467.
- Arpino G, Green SJ, Allred DC, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a southwest oncology group study. Clin Cancer Res 2004;10:5670-5676.

REFERENCE: Systemic Adjuvant Therapy

- Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive,node-positive breast cancer. J Clin Oncol 2000;18:3471-3479.
- De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res 2005;11:4741-4748.
- Eppenberger-Castori S, Kueng W, Benz C, et al. Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay. J Clin Oncol 2001;19:645-656.
- Knoop AS, Bentzen SM, Nielsen MM, et al. Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients. J Clin Oncol 2001;19:3376-3384.
- Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol 2000;27:46-52.
- Paik S, Shak S, Tang G, et al. Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 510.
- Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. Breast Cancer Res Treat 1998;52:65-77.
- Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human
- epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. J Clin Oncol 2008;26:1059-1065.
- Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771-784.
- Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717.
- Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805-816.
- Gray R, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [Abstract]. J Clin Oncol 2013;31(suppl):Abstract 5.
- Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinisinghormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007;369:1711-1723.
- Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 2005;23:5973-5982.

REFERENCE: Systemic Adjuvant Therapy

- Ejlertsen B, Mouridsen HT, Jensen MB, et al. Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. J Clin Oncol 2006;24:4956-4962.
- Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women.Cochrane Database Syst Rev 2009:CD004562.
- Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer 2003;39:1711-1717.
- Schmid P, Untch M, Wallwiener D, et al. Cyclophosphamide,methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive,premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). Anticancer Res 2002;22:2325-2332.
- Thomson CS, Twelves CJ, Mallon EA, Leake RE. Adjuvant ovarian ablation vs CMF chemotherapy in premenopausal breast cancer patients: trial update and impact of immunohistochemical assessment of ER status. Breast 2002;11:419-429.
- von Minckwitz G, Graf E, Geberth M, et al. CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93). Eur J Cancer 2006;42:1780-1788.
- Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst 2003;95:1833-1846.
- Puhalla S, Brufsky A, Davidson N. Adjuvant endocrine therapy for premenopausal women with breast cancer. Breast 2009;18 Suppl 3:S122-130.
- Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breastcancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol 2006;24:5664-5671.
- Boccardo F, Rubagotti A, Amoroso D, et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. boccardo@hp380.ist.unige.it. J Clin Oncol 2000;18:2718-2727.
- Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-118.
- Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment(Intergroup Exemestane Study): a randomised controlled trial. Lancet
- 2007;369:559-570.
- Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol 2007;25:2664-2670.
- Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97:1262-1271.

REFERENCE: Systemic Adjuvant Therapy

- Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45-53.
- Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747-2757.
- Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359:2131-2139.
- Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex,Tamoxifen, Alone or in Combination) trial after completion of 5 years‘ adjuvant treatment for breast cancer. Lancet 2005;365:60-62.
- Duffy S, Jackson TL, Lansdown M, et al. The ATAC ('Arimidex',Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment.Hum Reprod 2006;21:545-553.
- Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 2004;22:4261-4271.
- Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 2008;26:1051-1057.
- Dowsett M, Cuzick J, Howell A, Jackson I. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvantendocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination'(ATAC) trial. Br J Cancer 2001;85:317-324.
- Buzdar AU, Guastalla JP, Nabholtz JM, et al. Impact of chemotherapy regimens prior to endocrine therapy: Results from the ATAC (anastrozole and tamoxifen, alone or in combination) trial. Cancer 2006;107:472-480.
- Mouridsen H, Keshaviah A, Coates AS, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. J Clin Oncol 2007;25:5715-5722.
- Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 2009;20:1489-1498.
- Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361:766-776.
- Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 2005;23:5138-5147.
- Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17 Suppl 7:10-14. 301. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-1092.
- Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years‘ adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455-462.
- Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991-996.

REFERENCE: Systemic Adjuvant Therapy

- van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011;377:321-331.
- Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793-1802.
- Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol 2008;26:1948-1955.
- Ingle JN, Tu D, Pater JL, et al. Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. Ann Oncol 2008;19:877-882.
- Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629-3635.
- Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 2005;23:6931-6940.
- Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. The Lancet 2012.
- Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99:1845-1853.
- Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010;28:509-518.
- Smith IE, Dowsett M, Yap Y-S, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444-2447.
- Yu B, Douglas N, Ferin MJ, et al. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. Cancer 2010;116:2099-2105.
- Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2011.
- Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007;99:167-170.
- Available at: http://www.cypalleles.ki.se/.
- Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302:1429-1436.
- Leyland-Jones B, Regan M, Bouzyk M, et al. Outcome according to CYP2D6 genotype among postmenopausal women with endocrineresponsive early invasive breast cancer randomized in the BIG 1-98 trial [abstract]. Cancer Res 2010;70(24 Suppl):Abstract nr S1-8.
- Rae J, Drury S, Hayes D, et al. Lack of Correlation between Gene Variants in Tamoxifen Metabolizing Enymes with Primary Endpoints in the ATAC Trial [abstract] Cancer Res 2010;70(24 Suppl):Abstract S1-7.

REFERENCE: Systemic Adjuvant Therapy

- Higgins MJ, Stearns V. Pharmacogenetics of endocrine therapy for breast cancer. Annu Rev Med 2011;62:281-293.
- Visvanathan K, Chlebowski RT, Hurley P, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol 2009;27:3235-3258.
- Erban JK, Lau J. On the toxicity of chemotherapy for breast cancer--the need for vigilance. J Natl Cancer Inst 2006;98:1096-1097.
- Henderson I, Berry D, Demetri G, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976-983.
- Mamounas E, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 2005;23:3686-3696.
- Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dosedense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-1439.
- Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node positive or high risk node negative breast cancer [abstract]. San Antonio Breast Cancer Symposium 2005:Abstract 48.
- Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: Results of Intergroup Trial E1199 [abstract]. J Clin Oncol 2007;25 (Suppl_18) Abstract 516.
- Sparano J, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663-1671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18420499.
- Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735. J Clin Oncol 2009;27:1177-1183.
- Bang SM, Heo DS, Lee KH, et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000;89:2521-2526.
- Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifennonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8:1483-1496.
- Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicincyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15:1858-1869.
- Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352:930-942.

REFERENCE: Systemic Adjuvant Therapy

- Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994;330:1253-1259.
- Menard S, Valagussa P, Pilotti S, et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph nodepositive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol 2001;19:329-335.
- Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330:1260-1266.
- Watanabe T, Kuranami M, Inoue K, et al. Phase III trial comparing 4-cycle doxorubicin plus cyclophosphamide followed by 4-cycle taxan with 8-cycle taxan as adjuvant therapy for node-positive breast cancer: Results of N-SAS-BC02 trial [abstract]. J Clin Oncol 2009;27(Suppl
- 15):Abstract 516.
- Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103-3110.
- Levine M, Pritchard K, Bramwell V, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. J Clin Oncol 2005;23:5166-5170..
- Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 Randomized Trial. J Clin Oncol 2001;19:602-611.
- Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 2009;373:1681-1692.
- Martin M, Rodriguez-Lescure A, Ruiz A, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or
- followed by Paclitaxel for early breast cancer. J Natl Cancer Inst 2008;100:805-814.
- Samuel J, Wilson J, Bandos H, et al. NSABP B-36: A randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin andcyclophosphamide (AC) in patients (pts) with node-negative breast cancer {abstract]. San Antonio Breast Cancer Symposium. Oral Presentation Abstract S3-02 2014.
- Sparano JA ZF, Martino S, et al. Ten year update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary nodepositive or high-risk node-negative breast cancer [abstract]. SanAntonio Breast Cancer Symposium. Oral Presentation Abstract S3-03.2014
- Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302-2313.
- Swain SM, Jeong J-H, Geyer CE, et al. NSABP B-30: definitive analysis of patient outcome from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer [abstract]. Cancer Research 2009;69 (Suppl_1):Abstract 75.

REFERENCE: Systemic Adjuvant Therapy

- Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055-2065.
- Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med 2005;353:1652-1654.
- Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol 2009;27:5685-5692.
- Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366- 3373.
- Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011;12:236-244.
- Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231-1238.
- Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811-7819.
- Geyer CE, Jr., Bryant JL, Romond EH, et al. Update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)->paclitaxel (T) vs. AC->T with trastuzumab (H) [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 581.
- Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumabrelated cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525-3533.
- Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369:29-36. 358. Spielmann M, Roché H, Delozier T, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol 2009;27:6129-6134.
- Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol 2013;14:741-748.
- Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 2013;382:1021-1028. 361. Chia S, Norris B, Speers C, et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol 2008;26:5697-5704.
- Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller.J Clin Oncol 2009;27:5700-5706.

REFERENCE: Systemic Adjuvant Therapy

- O'Sullivan C, Holmes E, Spielmann M, et al. The prognosis of small HER2+ breast cancers: A meta-analysis of the randomized trastuzumab trials [abstract]. San Antonio Breast Cancer Symposium Meeting Abstracts 2013:Abstract S 6-03
- Zhou Q, Yin W, Du Y, Lu J. For or against Adjuvant Trastuzumab for pT1a-bN0M0 Breast Cancer Patients with HER2-Positive Tumors: A Meta-Analysis of Published Literatures. PLoS One 2014;9:e83646.
- Tolaney S, Barry W, Dang C, et al. A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC) [abstract]. San Antonio Breast Symposium Meeting Abstract 2013:Abstract S 1-04 (Oral Presentation).
- Piccart-Gebhart M HA, de Azambuja E, et al. . The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2- positive breast cancer. Survival follow-up analysis of the NeoALTTO study (BIG 1-06) [abstract]. SABCS 2013:Abstract S1–01.
- Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
- Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracyclinecontaining and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-2284.
- Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T->L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). ASCO Meeting Abstracts 2014;32:LBA4.
- Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 2009;27:5693-5699.
- Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. J Clin Oncol 2007;25(Suppl 18):Abstract 512.
- Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 2008;19:1090-1096.
- Swain S, Kim S-B, Cortes J, et al. Confirmatory overall survival (OS) analysis of CLEOPATRA: a randomized, double-blind, placebocontrolled Phase III study with pertuzumab (P), trastuzumab (T), and docetaxel (D) in patients (pts) with HER2-positive first-line (1L)metastatic breast cancer (MBC). Cancer Research 2012;72:P5-18-26.
- von MG, Baselga J, Bradbury I, et al. Adjuvant Pertuzumab and Herceptin IN IniTial TherapY of Breast Cancer: APHINITY (BIG 4–11/BO25126/TOC4939g) [abstract]. Cancer Res 2011; 71(Suppl 24):Abstract OT1-02-04.
- A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (Clinical Trial ID: NCT01358877).

REFERENCE: Systemic Adjuvant Therapy

- **Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-141.**
- **von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial Lancet Oncol 2014;15:747-756.**
- **Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance) [abstract]. Journal of Clinical Oncology 2014.**

REFERENCE: Stage III Invasive Breast Cancer

- Aukema TS, Straver ME, Peeters MJ, et al. Detection of extraaxillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer 2010;46:3205-3210.
- Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 2008;26:4746-4751.
- Groheux D, Moretti JL, Baillet G, et al. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. Int J Radiat Oncol Biol Phys 2008;71:695-704.
- van der Hoeven JJM, Krak NC, Hoekstra OS, et al. 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. J Clin Oncol 2004;22:1253-1259.
- Niikura N, Costelloe CM, Madewell JE, et al. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist 2011;16:1111-1119.
- Morris PG, Lynch C, Feeney JN, et al. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. J Clin Oncol 2010;28:3154-3159.
- Alessio AM, Kinahan PE, Cheng PM, et al. PET/CT scanner instrumentation, challenges, and solutions. Radiol Clin North Am
- 2004;42:1017-1032.
- Wong TZ, Paulson EK, Nelson RC, et al. Practical approach to diagnostic CT combined with PET. AJR Am J Roentgenol
- 2007;188:622-629.
- Hortobagyi GN, Singletary SE, Strom EA. Locally advanced breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast. Philadelphia: Lippincott Williams & Wilkins;2004.
- Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA 1994;271:1587-1592.
- Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271:1593-1597.
- Smith TJ, Davidson NE, Schapira DV, et al. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. J Clin Oncol 1999;17:1080-1082.
- Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1865-1878.
- Kirova YM, Stoppa-Lyonnet D, Savignoni A, et al. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. Eur J Cancer 2005;41:2304-2311.
- Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328-2335.
- Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multiinstitutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437-2443.

REFERENCE: Stage III Invasive Breast Cancer

- ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006;107:1475-1478.
- Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-2063.
- Boekhout AH, Vincent AD, Dalesio OB, et al. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J ClinOncol 2011;29:3862-3868.
- Kaplan M, Mahon S, Cope D, et al. Putting evidence into practice: evidence-based interventions for hot flashes resulting from cancer therapies. Clin J Oncol Nurs 2011;15:149-157.
- Bordeleau L, Pritchard KI, Loprinzi CL, et al. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol 2010;28:5147-5152.
- Garber K. Tamoxifen pharmacogenetics moves closer to reality. J Natl Cancer Inst 2005;97:412-413.
- Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30-39.
- Henry NL, Stearns V, Flockhart DA, et al. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression.Am J Psychiatry 2008;165:1251-1255.
- Ahern TP, Pedersen L, Cronin-Fenton DP, et al. No increase in breast cancer recurrence with concurrent use of tamoxifen and some CYP2D6-inhibiting medications. Cancer Epidemiol Biomarkers Prev 2009;18:2562-2564.
- Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-497.
- Dayes IS, Whelan TJ, Julian JA, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. J Clin Oncol 2013;31:3758-3763. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. Ann Plast Surg 2007;59:464-472.
- Li CI, Daling JR, Porter PL, et al. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. J Clin Oncol 2009;27:5312-5318.
- Pierce JP, Stefanick ML, Flatt SW, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol 2007;25:2345-2351.
- Chlebowski RT BG, et al. . Final survival analysis from the randomized Women's Intervention Nutrition Study (WINS) evaluating dietary intervention as adjuvant breast cancer therapy [abstract]. San Antonio Breast Cancer Symposium 2014;Abstract S5-08.
- Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. Human Reproduction Update 2009;15:323-339.
- Moran MS, Colasanto JM, Haffty BG, et al. Effects of breastconserving therapy on lactation after pregnancy. Cancer J 2005;11:399-403.
- Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Eubank WB, Mankoff D, Bhattacharya M, et al. Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. AJR Am J Roentgenol 2004;183:479-486.
- Moon DH, Maddahi J, Silverman DH, et al. Accuracy of wholebody fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 1998;39:431-435.
- Arslan C, Sari E, Aksoy S, Altundag K. Variation in hormone receptor and HER-2 status between primary and metastatic breast cancer: review of the literature. Expert Opin Ther Targets 2011;15:21-30.
- Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 2010;15:1164-1168.
- Bogina G, Bortesi L, Marconi M, et al. Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Arch 2011;459:1-10.
- Fabi A, Di Benedetto A, Metro G, et al. HER2 protein and gene variation between primary and metastatic breast cancer: significance and impact on patient care. Clin Cancer Res 2011;17:2055-2064.
- Karlsson E, Lindström LS, Wilking U, et al. Discordance in hormone receptor status in breast cancer during tumor progression [abstract]. J Clin Oncol 2010;28:(15_Suppl):Abstract 1009.
- Sari E, Guler G, Hayran M, et al. Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Med Oncol 2011;28:57-63.
- Simmons C, Miller N, Geddie W, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009;20:1499-1504.
- Gong Y, Booser DJ, Sneige N. Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer 2005;103:1763-1769.
- Tapia C, Savic S, Wagner U, et al. HER2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Res 2007;9.
- Lindstrom LS, Karlsson E, Wilking UM, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 2012;30:2601-2608.
- Dieci MV, Barbieri E, Piacentini F, et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Ann Oncol 2013;24:101-108.
- Aurilio G, Disalvatore D, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. Eur J Cancer 2014;50:277-289.
- Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy:implications for postoperative irradiation. J Clin Oncol 2000;18:2817-2827.
- van Tienhoven G, Voogd AC, Peterse JL, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG- 82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur J Cancer 1999;35:32-38.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Cox CE, Furman BT, Kiluk JV, et al. Use of reoperative sentinel lymph node biopsy in breast cancer patients. J Am Coll Surg 2008;207:57-61.
- Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial.Lancet Oncol 2014;15:156-163.
- Higgins MJ, Wolff AC. Therapeutic options in the management of metastatic breast cancer. Oncology (Williston Park) 2008;22:614-623.
- Gralow JR, Biermann JS, Farooki A, et al. NCCN task force report: Bone health in cancer care. J Natl Compr Canc Netw 2009;7 Suppl 3:1-1.
- Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042-4057.
- Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol 2010;28:5132-5139.
- Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165-176.
- Woo S-B, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144:753-761.
- Ali SM, Esteva FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. J Clin Oncol 2001;19:3434-3437.
- Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 2001;91:1191-1200.
- Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial.The Aredia Multinational Cooperative Group. J Clin Oncol 1996;14:2552-2559.
- Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998;16:2038-2044.
- Theriault RL. The role of bisphosphonates in breast cancer. J Natl Compr Canc Netw 2003;1:232-241.
- Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17:846-854.
- Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III,double-blind, comparative trial. Cancer J 2001;7:377-387.
- Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;100:36-43.
- Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004;40:1704-1712.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 1996;335:1785-1791.
- Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term followup of two randomized, placebo-controlled trials. Cancer 2000;88:1082-1090.
- McLachlan SA, Cameron D, Murray R, et al. Safety of oral ibandronate in the treatment of bone metastases from breast cancer :long-term follow-up experience. Clin Drug Investig 2006;26:43-48.
- Pecherstorfer M, Rivkin S, Body J-J, et al. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. Clin Drug Investig 2006;26:315-322.
- Hortobagyi GN, Lipton A, Chew HK, et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. ASCO Meeting Abstracts
- Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98:1735-1744.
- Wilkinson GS, Kuo Y-F, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst 2007;99:1016-1024.
- Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a metaanalysis of four randomized trials. J Clin Oncol 2001;19:343-353.
- Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18:3748-3757.
- Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000;18:3758- 3767.
- Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 2008;26:4883-4890.
- Vergote I, Bonneterre J, Thurlimann B, et al. Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Eur J Cancer 2000;36 Suppl 4:S84-85.
- Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women.Cochrane Database Syst Rev 2009.
- Howell A, Robertson JFR, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrinetreatment. J Clin Oncol 2002;20:3396-3403.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20:3386-3395.
- Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol 2009;27:4530-4535.
- Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat 2012;136:503-511.
- Robertson J, Llombart-Cussac A, Felti D, et a. Fulvestrant 500 mg versus anastrozole as first-line treatment for advanced breast cancer: Overall survival from the phase II ‘FIRST’ study [abstract]. 2014; San Antonio Breast Cancer Symposium:Abstract S6-04. Available at:
- Ingle JN, Suman VJ, Rowland KM, et al. Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032. J Clin Oncol 2006;24:1052-1056.
- Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664-1670.
- Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positiveadvanced breast cancer. J Clin Oncol 2010;28:4594-4600.
- Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 2014;106:djt337.
- Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012;30:1919-1925.
- Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med 2012;367:435-444.
- Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer(SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 2013;14:989-998.
- Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001;19:3357-3366.
- Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 1998;83:1142-1152.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35.
- Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27:5538-5546.
- Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27:5529-5537.
- Bachelot T, Bourgier c, Cropet C, et al. TAMRAD: A GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast Cancer (MBC) with prior exposure to aromatase inhibitors (AI) [abstract]. Cancer Res 2010;70(24 Supplement):Abstract: S1-6
- Chow L, Sun Y, Jassem J, et al. Phase 3 study of temsirolimus with letrozole or letrozole alone in postmenopausal women with locally advanced or metastatic breast cancer. Breast Cancer Res Treat. 2006;100(Suppl 1):6091.
- Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther
- 2013;30:870-884.
- Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-529.
- Pritchard KI, Burris HA, 3rd, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer 2013;13:421-432 e428.
- Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J ClinOncol 1996;14:2000-2011.
- Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 1998;16:453-461.
- Lonning PE, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. J Clin Oncol 2000;18:2234-2244.
- Albain KS, Nag S, Calderillo-Ruiz G, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival [Abstract]. J Clin Oncol 2004;22:Abstract 510.
- Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2005.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracyclinepretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812-2823.
- Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol 2003;21:588-592.
- Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 2011;29:2144-2149.
- Falkson G, Gelman RS, Pandya KJ, et al. Eastern Cooperative Oncology Group randomized trials of observation versus maintenance therapy for patients with metastatic breast cancer in complete remission following induction treatment. J Clin Oncol 1998;16:1669-1676.
- Muss HB, Case LD, Richards F, et al. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. N Engl J Med 1991;325:1342-1348.
- Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breastcancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914-923.
- Kaufman P, Awada A, Twelves C, et al. A phase III, open-label,randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes [abstract]. Cancer Res 2012;72(Suppl 24):Abstract S6-6.
- Roche H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. J Clin Oncol 2007;25:3415-3420.
- Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. J Clin Oncol 2007;25:3399- 3406.
- Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol 2007;25:3407-3414.
- Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-2676.
- Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28:3239-3247.
- Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC) [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 1005.
- Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer.J Clin Oncol 2011;29:1252-1260.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- O'Shaughnessy J, Miles D, Gray RJ, et al. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC) [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 1005.
- BRIEFING BOOK, ONCOLOGY DRUGS ADVISORY COMMITTEE MEETING, AVASTIN (Bevacizumab). Genentech, Inc., A Member of the Roche Group; 2010.
- Seidman A, Berry DA, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008;26:1642-1649.
- Carlson RW, Moench SJ, Hammond ME, et al. HER2 testing in breast cancer: NCCN Task Force report and recommendations. J Natl Compr Canc Netw 2006;4 Suppl 3:1-22.
- Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in the breast intergroup trial N9831. J Natl Cancer Inst 2002;94:855-857.
- Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118-145.
- Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-119.
- Ewer M, Baselga J, Clark E, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study [abstract]. J Clin Oncol 2012;30 (Suppl_15):Abstract 533.
- Cortés J, Baselga J, Im Y, et al. Quality of life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer [abstract]. J Clin Oncol 2012 30 (Suppl_15) Abstract 598
- Datko F, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer [abstract]. Cancer Research 2012;72:Abstract P5-18-20.
- Paclitaxel, trastuzumab, and pertuzumab in the treatment of metastatic HER2-positive breast cancer (Clinical Trial ID: NCT01276041).
- Perez E, Lopez-Vega J, Mastro L, et al. A combination of pertuzumab, trastuzumab, and vinorelbine for first-line treatment of patients with HER2-positive metastatic breast cancer: An open-label, two-cohort, phase II study (VELVET) [abstract]. J Clin Oncol 2012;30 (Suppl_15):Asbtract TPS653.
- Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965-972.
- Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786-2792.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Schaller G, Bangemann N, Weber J, et al. Efficacy and safety of trastuzumab plus capecitabine in a German multicentre phase II study of pre-treated metastatic breast cancer [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 717.
- Yamamoto D, Iwase S, Kitamura K, et al. A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial. Cancer Chemother Pharmacol 2008;61:509-514.
- Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-1221.
- Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853-3858.
- von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2- positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006.
- Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05) [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 1025.
- Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783- 1791.
- Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138-1144.
- Cortes J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30:1594-1600.
- Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-2743.
- Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist 2010;15:924-934.
- Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124-1130.
- Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol 2012;30:2585-2592.
- Hortobagyi GN. Multidisciplinary management of advanced primary and metastatic breast cancer. Cancer 1994;74:416-423.
- Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006;13:776-782.

REFERENCE: Stage IV Metastatic or Recurrent Breast Cancer

- Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002;132:620-626.
- Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 2008;15:1696-1702.
- Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006;24:2743-2749. Morrow M, Goldstein L. Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? J Clin Oncol 2006;24:2694-2696.
- Olson JA, Marcom PK. Benefit or bias? The role of surgery to remove the primary tumor in patients with metastatic breast cancer. Ann Surg 2008;247:739-740.
- Badwe R, Parmar V, Hawaldar R, et al. Surgical removal of primary breast tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: a randomized controlled trial. Presented at: 2013 [abstract]. San Antonio Breast Cancer Symposium 2013:Abstract S2-02.
- Soran A, Ozmen V, Ozbas S, et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) [abstract]. San Antonio Breast Cancer Symposium 2013:Abstract S2-03.
- Jones EL, Oleson JR, Prosnitz LR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. J Clin Oncol 2005;23:3079-3085.
- Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996;35:731-744.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version1.1). Eur J Cancer 2009;45:228-247.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214.
- Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol 2014;32:3483-3489.

REFERENCE: Special Situations

- Sakorafas GH, Blanchard K, Sarr MG, Farley DR. Paget's disease of the breast. Cancer Treat Rev 2001;27:9-18.
- Kollmorgen DR, Varanasi JS, Edge SB, Carson WE. Paget's disease of the breast: a 33-year experience. J Am Coll Surg 1998;187:171-177.
- Marcus E. The management of Paget's disease of the breast. Curr Treat Options Oncol 2004;5:153-160.
- Morrogh M, Morris EA, Liberman L, et al. MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. J Am Coll Surg 2008;206:316-321.
- Frei KA, Bonel HM, Pelte M-F, et al. Paget disease of the breast: findings at magnetic resonance imaging and histopathologic correlation.Invest Radiol 2005;40:363-367.
- Bijker N, Rutgers EJ, Duchateau L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer 2001;91:472-477.
- Kawase K, Dimaio DJ, Tucker SL, et al. Paget's disease of the breast: there is a role for breast-conserving therapy. Ann Surg Oncol 2005;12:391-397.
- Marshall JK, Griffith KA, Haffty BG, et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. Cancer 2003;97:2142-2149.
- Pierce LJ, Haffty BG, Solin LJ, et al. The conservative management of Paget's disease of the breast with radiotherapy. Cancer 1997;80:1065-1072.
- Singh A, Sutton RJ, Baker CB, Sacks NP. Is mastectomy overtreatment for Paget's disease of the nipple? Breast 1999;8:191-94.
- Laronga C, Hasson D, Hoover S, et al. Paget's disease in the era of sentinel lymph node biopsy. Am J Surg 2006;192:481-483.
- Sukumvanich P, Bentrem DJ, Cody HS, et al. The role of sentinel lymph node biopsy in Paget's disease of the breast. Ann Surg Oncol2007;14:1020-1023.
- Telli ML, Horst KC, Guardino AE, et al. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw 2007;5:324-330.
- Anderson BO, Lawton TJ, Lehman CD, Moe RE. Phyllodes tumors. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast (ed 3rd). Philadelphia: Lippincott Williams & Wilkins; 2004.
- Salvadori B, Cusumano F, Del Bo R, et al. Surgical treatment of phyllodes tumors of the breast. Cancer 1989;63:2532-2536.
- Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene 2001;20:4621-4628.
- Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer 2000;89:1502-1511.
- Mangi AA, Smith BL, Gadd MA, et al. Surgical management of phyllodes tumors. Arch Surg 1999;134:487-492.
- Pandey M, Mathew A, Kattoor J, et al. Malignant phyllodes tumor. Breast J 2001;7:411-416.
- Tse GMK, Lee CS, Kung FYL, et al. Hormonal receptors expression in epithelial cells of mammary phyllodes tumors correlateswith pathologic grade of the tumor: a multicenter study of 143 cases. Am J Clin Pathol 2002;118:522-526.

REFERENCE: Special Situations

- Smith LH, Dalrymple JL, Leiserowitz GS, et al. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. Am J Obstet Gynecol 2001;184:1504-1512.
- Gwyn K, Theriault R. Breast cancer during pregnancy. Oncology (Williston Park) 2001;15:39-46.
- Middleton LP, Amin M, Gwyn K, et al. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer 2003;98:1055-1060.
- Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. Radiology 2006;239:52-60.
- Kuerer HM, Gwyn K, Ames FC, Theriault RL. Conservative surgery and chemotherapy for breast carcinoma during pregnancy. Surgery 2002;131:108-110.
- Annane K, Bellocq JP, Brettes JP, Mathelin C. Infiltrative breast cancer during pregnancy and conservative surgery. Fetal Diagn Ther 2005;20:442-444.
- Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. Breast J 2008;14:250-254.
- Mondi MM, Cuenca RE, Ollila DW, et al. Sentinel lymph node biopsy during pregnancy: initial clinical experience. Ann Surg Oncol 2007;14:218-221.
- Filippakis GM, Zografos G. Contraindications of sentinel lymph node biopsy: are there any really? World J Surg Oncol 2007;5:10.
- Gentilini O, Cremonesi M, Trifiro G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004;15:1348-1351.
- Keleher A, Wendt R, Delpassand E, et al. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid.Breast J 2004;10:492-495.
- Pandit-Taskar N, Dauer LT, Montgomery L, et al. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med 2006;47:1202-1208.
- Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. Ann Oncol 2004;15:146-150.
- Johnson PH, Gwyn K, Gordon N, et al. The treatment of pregnant women with breast cancer and the outcomes of the children exposed to chemotherapy in utero [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 540.
- Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol 1989;16:337-346.
- Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. Pharmacol Ther 1997;74:207-220.
- Hahn KME, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 2006;107:1219-1226.
- Gainford MC, Clemons M. Breast cancer in pregnancy: are taxanes safe? Clinical Oncol (R Coll Radiol) 2006;18:159.
- Garcia-Manero M, Royo MP, Espinos J, et al. Pregnancy associated breast cancer. Eur J Surg Oncol 2009;35:215-218.
- Gonzalez-Angulo AM, Walters RS, Carpenter RJ, et al. Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. Clin Breast Cancer 2004;5:317-319.

REFERENCE: Special Situations

- Mir O, Berveiller P, Ropert S, et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol 2008;19:607-613.
- Bader AA, Schlembach D, Tamussino KF, et al. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. Lancet Oncol 2007;8:79-81.
- Fanale MA, Uyei AR, Theriault RL, et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clin Breast Cancer 2005;6:354-356.
- Pant S, Landon MB, Blumenfeld M, et al. Treatment of breast cancer with trastuzumab during pregnancy. J Clin Oncol 2008;26:1567- 1569.
- Sekar R, Stone PR. Trastuzumab use for metastatic breast cancer in pregnancy. Obstet Gynecol 2007;110:507-510.
- Shrim A, Garcia-Bournissen F, Maxwell C, et al. Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy--Case report and updated literature review. Reprod Toxicol 2007;23:611-613.
- Waterston AM, Graham J. Effect of Adjuvant Trastuzumab on Pregnancy. J Clin Oncol 2006;24:321-322.
- Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. Obstet Gynecol 2005;105:642-643.
- Witzel ID, Müller V, Harps E, et al. Trastuzumab in pregnancy associated with poor fetal outcome. Ann Oncol 2008;19:191-192.
- Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. Clin Breast Cancer 2006;7:339-341.
- Dawood, S, Cristofanilli M. What progress have we made in managing inflammatory breast cancer? Oncology 2007;21:673-679.
- Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: a review. J Clin Oncol 1992;10:1014-1024.
- Bertucci F, Finetti P, Rougemont J, et al. Gene expression profiling identifies molecular subtypes of inflammatory breast cancer. Cancer Res 2005;65:2170-2178.
- Van Laere SJ, Van den Eynden GG, Van der Auwera I, et al.Identification of cell-of-origin breast tumor subtypes in inflammatory breast cancer by gene expression profiling. Breast Cancer Res Treat 2006;95:243-255.
- Zell JA, Tsang WY, Taylor TH, et al. Prognostic impact of human epidermal growth factor-like receptor 2 and hormone receptor status in inflammatory breast cancer (IBC): analysis of 2,014 IBC patient cases from the California Cancer Registry. Breast Cancer Res 2009;11:R9.
- Parton M, Dowsett M, Ashley S, et al. High incidence of HER-2 positivity in inflammatory breast cancer. Breast 2004;13:97-103.
- Haagensen CD. Inflammatory Carcinoma. Diseases of the Breast.Philadelphia: WB Saunders; 1956:488-498.

REFERENCE: Special Situations

- Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. Cancer 2007;110:1436-1444.
- Panades M, Olivotto IA, Speers CH, et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol 2005;23:1941-1950.
- Dawood S, Ueno NT, Valero V, et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced breast cancer appear early: a large population-based study. Cancer 2011;117:1819-1826.
- Hance KW, Anderson WF, Devesa SS, et al. Trends in inflammatory breast carcinoma incidence and survival: the surveillance,epidemiology, and end results program at the National Cancer Institute.J Natl Cancer Inst 2005;97:966-975.
- Bleicher RJ, Morrow M. Inflammatory breast cancer: Still poorly characterized. The Dawood/Cristofanilli article reviewed. Oncology 2007;21:679-680.
- Nguyen DM, Sam K, Tsimelzon A, et al. Molecular heterogeneity of inflammatory breast cancer: a hyperproliferative phenotype. Clin Cancer Res 2006;12:5047-5054.
- Carkaci S, Macapinlac HA, Cristofanilli M, et al. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data. J Nucl Med 2009;50:231-238.
- Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. J Clin Oncol 2008;26:786-790.
- Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. Ann Surg Oncol 1997;4:452-461.
- Ueno NT, Buzdar AU, Singletary SE, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M. D. Anderson Cancer Center. Cancer Chemother Pharmacol 1997;40:321-329.
- Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, et al. Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M. D. Anderson Cancer Center experience. Clin Breast Cancer 2004;4:415-419.
- Kim T, Lau J, Erban J. Lack of uniform diagnostic criteria for inflammatory breast cancer limits interpretation of treatment outcomes: a systematic review. Clin Breast Cancer 2006;7:386-395.
- Hennessy BT, Gonzalez-Angulo AM, Hortobagyi GN, et al. Disease-free and overall survival after pathologic complete disease remission of cytologically proven inflammatory breast carcinoma axillary lymph node metastases after primary systemic chemotherapy. Cancer 2006;106:1000-1006.
- Dawood S, Broglio K, Gong Y, et al. Prognostic significance of HER-2 status in women with inflammatory breast cancer. Cancer 2008;112:1905-1911.
- Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. The Lancet 2010;375:377-384.
- Hurley J, Doliny P, Reis I, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 2006;24:1831-1838.

REFERENCE: Special Situations

- Burstein HJ, Harris LN, Gelman R, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. J Clin Oncol 2003;21:46-53.
- Limentani SA, Brufsky AM, Erban JK, et al. Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. J Clin Oncol 2007;25:1232-1238.
- Van Pelt AE, Mohsin S, Elledge RM, et al. Neoadjuvant trastuzumab and docetaxel in breast cancer: preliminary results. Clin Breast Cancer 2003;4:348-353.
- Boussen H, Cristofanilli M, Zaks T, et al. Phase II study to evaluate the efficacy and safety of neoadjuvant lapatinib plus paclitaxel in patients with inflammatory breast cancer. Journal of Clinical Oncology 2010;28:3248-3255.
- Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. Breast Dis 2005;22:67-73.
- Stearns V, Ewing CA, Slack R, et al. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 2002;9:235-242.
- Motwani SB, Strom EA, Schechter NR, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys 2006;66:76-82.
- Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM.Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 2008;247:732-738.
- Olson JA, Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol 2000;7:411-415.
- Varadarajan R, Edge SB, Yu J, et al. Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis. Oncology 2006;71:456-459.
- Schelfout K, Kersschot E, Van Goethem M, et al. Breast MR imaging in a patient with unilateral axillary lymphadenopathy and unknown primary malignancy. Eur Radiol 2003;13:2128-2132.
- Bhatia SK, Saclarides TJ, Witt TR, et al. Hormone receptor studies in axillary metastases from occult breast cancers. Cancer 1987;59:1170-1172.
- Bleicher RJ, Morrow M. MRI and breast cancer: role in detection, diagnosis, and staging. Oncology (Williston Park) 2007;21:1521-1528,1530; discussion 1530, 1532-1523.
- Stomper PC, Waddell BE, Edge SB, Klippenstein DL. Breast MRI in the Evaluation of Patients with Occult Primary Breast Carcinoma. Breast J 1999;5:230-234.
- Buchanan CL, Morris EA, Dorn PL, et al. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol 2005;12:1045-1053.

References for Radiotherapy

- Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy forbreast cancer: 5-year results for local control and overall survival from theTARGIT-A randomised trial. Lancet. 2014;383(9917): 603-613. Available at: https://pubmed.ncbi.nlm.nih.gov/24224997/
- Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-1277. Available at: https://pubmed.ncbi.nlm.nih.gov/24225155/
- Correa C, Harris EE, Leonardi MC et al, Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol*. 2017;7:73–79. Available at: https://pubmed.ncbi.nlm.nih.gov/27866865/
- Smith BD, Arthur DW, Buchholz TA et al, Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74:987–1001. Available at: https://pubmed.ncbi.nlm.nih.gov/19545784/
- Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol*. 2018;8(3):145-152. Available at: https://pubmed.ncbi.nlm.nih.gov/29545124/
- National Comprehensive Cancer Network. Breast Cancer (Version 4, May 8, 2020). https://www.nccn.org/professionals/physician_gls/pdf/breast. pdf. Accessed June 20, 2020
- Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24:3381-3387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16801628.
- Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355:528-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10683002.
- Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015;16:47-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25500422.
- Moran MS, Zhao Y, Ma S, et al. Association of Radiotherapy Boost for Ductal Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy. JAMA Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28358936.
- Gilleard O, Goodman A, Cooper M, et al. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World J Surg Oncol 2008;6:61-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18564426.

- Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving SurgeryWith Whole-Breast Irradiation in Ductal Carcinoma in Situ. Pract Radiat Oncol 2016;6:287-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27538810.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa022152.
- Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22019144.
- Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.Available at: http://www.ncbi.nlm.nih.gov/pubmed/24516019.
- .
- Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21304082.
- Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303-1310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25439688.
- Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26:2085-2092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18285602.
- Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18355913.
- Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426-432; discussion 432-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20739842

- **Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18356109**
- **Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513-520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20147717.**
- **Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:307-316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26200977.**
- **Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382-2387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23690420.**
- **Kunkler IH, Williams LJ, Jack WJ, et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 2015;16:266-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25637340.**
- **Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004;22:4691-4699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15570071.**
- **.**
- **Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006;24:2268-2275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16618947**