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## Overview of Breast Cancer and Treatment Options

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### Objectives

- Discuss breast cancer statistics
- Outline the timeline of a breast cancer diagnosis through treatment and survivorship
- Explain common terminology for a breast cancer diagnosis
- Describe surgical options for patients undergoing treatment for breast cancer
- Identify for which patients radiation is recommended
- Identify for which patients chemotherapy is recommended
- Identify for which patients targeted and/or endocrine therapy is recommended

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### Statistics from the American Cancer Society (ACS)

- Most common cancer in American women (except skin cancers).
- Second leading cause of cancer death in women (lung is #1).
- Average risk of a woman in the U.S. developing breast cancer over their lifetime is approximately 13%. (1 in 8).
- In recent years, incidence rates have increased by 0.5% each year.
- Death rates have been steady in women younger than 50 but have continued to decrease in older women.



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### Statistics Continued (American Cancer Society)

Estimated new cases, 2021	Estimated deaths, 2021
By cancer type, both sexes combined	By cancer type, both sexes combined
Breast 284,200	Lung and bronchus 131,880
Prostate 248,530	Colorectum 52,980
Lung and bronchus 235,760	Pancreas 48,220
Colorectum 149,500	Breast 44,130
Melanoma of the skin 106,110	Prostate 34,130
Urinary bladder 83,730	Liver and intrahepatic bile duct 30,230

EXPAND TO SEE ALL DATA

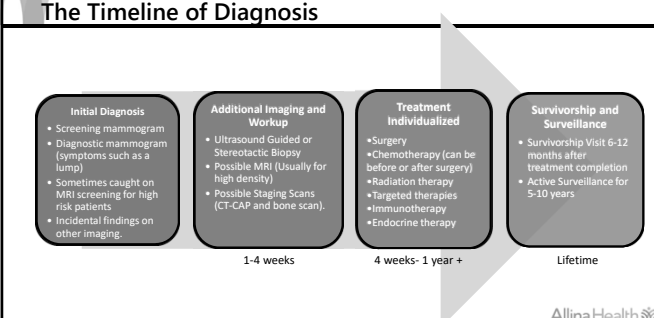
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### Genetic Statistics

- Only about 10% of all breast cancer diagnoses are related to having a genetic predisposition
- Genetic testing for breast cancer specific genes is usually completed via a multi-gene panel. 19-23 genes
  - BRCA1: absolute risk >60% (predisposition to triple negative disease)
  - BRCA2: absolute risk >60% (predisposition to ER+ disease)
  - Others: **ATM** (15-40%), **BARD1** (15-40%), **CDH1** (41-60%), **CHEK2** (15-40%), **MSH2; MSH1; MSH6; PMS2; EPCAM** (<15%), **NF1** (15-40%), **PALB2** (41-60% predisposition to triple neg), **PTEN** (40-60%), **RAD51C** (15-40%, ER/PR-), **RADS1D** (15-40%, ER/PR-) **STK11** (40-60%), **TP53** (>60%, triple +)

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### The Timeline of Diagnosis



Initial Diagnosis	Additional Imaging and Workup	Treatment Individualized	Survivorship and Surveillance
<ul style="list-style-type: none"> <li>• Screening mammogram</li> <li>• Diagnostic mammogram (symptoms such as a lump)</li> <li>• Sometimes caught on MRI screening for high risk patients</li> <li>• Incidental findings on other imaging.</li> </ul>	<ul style="list-style-type: none"> <li>• Ultrasound Guided or Stereotactic Biopsy</li> <li>• Possible MRI (Usually for high density)</li> <li>• Possible Staging Scans (CT-CAPI and bone scan).</li> </ul>	<ul style="list-style-type: none"> <li>• Surgery</li> <li>• Chemotherapy (can be before or after surgery)</li> <li>• Radiation therapy</li> <li>• Targeted therapies</li> <li>• Immunotherapy</li> <li>• Endocrine therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Survivorship Visit 6-12 months after treatment completion</li> <li>• Active Surveillance for 5-10 years</li> </ul>
1-4 weeks	1-4 weeks	4 weeks - 1 year +	Lifetime

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### Anatomy Review

- Lobules: Where breast milk is made.
- Ducts: Carry milk from lobules to the nipple.
- Lymph nodes: catch lymphatic drainage from the breast
- Breast Parenchyma: Connective tissues of the breast (includes fatty tissue).

Breast cancer starts in either the ducts or the lobules or both. Ductal is more common.

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### How cancer is found on a mammogram

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### 2D vs. 3D mammograms (tomosynthesis)

- 2D takes one picture from each angle
- 3D takes a series of nearly 400 pictures that allows the radiologist to scroll through images and see a clearer picture.
- 3D works better for higher breast density.
- Studies have shown that 3D does catch a percentage more cancers than 2D but also that it significantly reduces the number of call backs for women (additional imaging, biopsies, etc.)
- 3D is still not covered by some insurance.

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### Biopsy Results

- ADH/ALH: Not cancer. Not a pre-cancer. Higher risk for breast cancer in either breast in any location; about 1% per year. Requires excisional biopsy (ADH only) to rule out a co-existing breast cancer. (20%). Recommended to follow in high risk clinic. Can consider medications to reduce risk of breast cancer.
- DCIS: Stage 0 breast cancer. Contained in ducts. Only check estrogen receptor. Would not need chemotherapy. (LCIS is generally NOT considered cancer. It's generally a higher risk type of atypia).
- DCIS that has just started to spread to surrounding breast tissue. All receptors are checked. Stage 1(mi).
- IDC/ILC: Breast cancer that has spread to surrounding areas of breast. Sometimes includes DCIS, sometimes not. All receptors are checked. Can be stages 1-4; depends on overall size and other factors. Invasive does not necessarily imply metastatic (spread to other areas of the body).

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### Inflammatory Breast Cancer

- Breast cancer that invades the dermis (skin).
- Typically presents with erythema and swelling encompassing over 1/3 of the patient's breast. Peau d'orange appearance is hallmark sign.
- It's common to have a "negative" mammogram. Usually diagnosed on skin biopsy.
- In 1/3 of cases, metastasis is already present
- Requires aggressive treatment

Inflammatory breast cancer

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### Common Terminology - Grade

Grade 1

Grade 2

Grade 3

One means of predicting the behavior of the tumor cells. AllinaHealth

### Common Terminology – Hormone Receptors

#### Hormone Receptor Status in Breast Cancer

#### Receptor Testing:

- Estrogen Receptor (ER)
- Progesterone Receptor (PR)
- Positive = overexpression
- Negative = normal expression
- Presence of estrogen and/or progesterone in contact with receptors drives cancer growth.

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### Common Terminology – HER2

#### Human Epidermal Growth Factor Receptor 2 (HER2)

- Protein involved in normal cell growth
- Positive = overexpression
- Negative = normal expression
- Targeted therapy option for HER2 +

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### Common Terminology – Breast Cancer Subtypes

All Cases

Hormone Receptor Positive/Negative

**HR Negative**

HR - / HER2 -  
“Triple Negative”  
13% of all cases

HR - / HER2 +  
Least common  
5% of all cases

**HR Positive**

HR + / HER2+  
“Triple Positive”  
10% of all cases

HR + / HER2 -  
Most Common  
73% of all cases

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### Common Terminology - Staging

#### Staging

- expedites the exchange of data and provides a means of comparing treatment results based on common criteria
- describes the how extensive the breast cancer is and includes:
  - size of tumor
  - number and size of lymph node(s) involved
  - spread to distant parts of the body
  - biomarkers
- is done both before (clinical stage) and after a patient undergoes surgery (pathologic stage)
- 4 stages of invasive breast cancer

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### Common Terminology - Staging

Stage	Primary Tumor	Nodes	Metastases
Stage 1A	≤ 20 mm	None	None
Stage 1B	≤ 20 mm	Nodal Micrometastases (>0.2 mm <2.0 mm)	None
Stage IIA	≤ 20 mm	N1	None
Stage IIB	> 20 mm ≤ 50 mm	N1	None
Stage IIIA	≤ 50 mm	N2	None
Stage IIIB	> 50 mm	N1 or N2	None
Stage IIIC	Extension to chest wall and/or skin	NO - N2	None
Stage IIIC	Any size	N3	None
Stage IV	Any size	Any involvement	Detectable

NO = no regional lymph node metastasis  
 N1 = 1-3 axillary lymph nodes involved and/or internal mammary nodes with metastases detected by biopsy  
 N2 = 4-9 axillary lymph nodes involved or clinically detected internal mammary nodes in the absence of axillary nodal involvement  
 N3 = ≥ 10 axillary lymph nodes involved, or infraclavicular or lymph nodes, or clinically detected internal mammary lymph nodes with axillary involvement, or ≥ 3 axillary nodes with internal mammary nodes detected by biopsy, or in ipsilateral supraclavicular lymph nodes.

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### Surgical Treatment of Breast Cancer

- Excisional biopsy
  - Done for a definitive tissue diagnosis when initial sampling on needle biopsy is insufficient, inconclusive (discordant), or when there is a higher chance of malignancy (ex: atypical ductal hyperplasia).
- Lumpectomy (breast conserving therapy; partial mastectomy) (more information on upcoming slide)
- Mastectomy (removal of entire breast/tissue) (more information on upcoming slide)
- Sentinel lymph node biopsy (more information on upcoming slides)
- Axillary dissection
  - Removal of all the lymph nodes in the axilla (levels 1 and 2). Not done as much anymore but is still sometimes required. (Z11)
- Modified radical mastectomy
  - Mastectomy and axillary dissection completed at same time as a planned operation. Done for patients with positive lymph nodes after neoadjuvant chemotherapy, inflammatory breast cancer, and other situations depending on clinical judgement.
- Palliative Mastectomy
  - Mastectomy that is completed for patients with Stage IV disease and not for curative treatment. Often done for fungating tumors.

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### Lumpectomy (AKA breast conserving therapy or partial mastectomy)

The tumor is removed with a rim of normal breast tissue.

Postoperative appearance depends on the amount of tissue removed, but there will be a small scar and often an indentation in the breast.

Margins

Lumpectomy/partial mastectomy

- Will often include a separate incision at the axilla for sentinel lymph node biopsy (SLNbx)
- Exceptions:
  - SLNbx not completed for DCIS
  - Sometimes completed through same incision if close to same area.
- May require margin re-excision if cancer is seen at/near edge of specimen.

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### Mastectomy

- Removal of entire breast.
- Can be with or without reconstruction.
- Reconstruction can be autologous (tissue based) or implant based.
- A lot of women are offered a choice between a lumpectomy or mastectomy.
- Mastectomy required when:
  - Significant disease
  - Prior radiation (recurrence)
  - Persistent positive margins on lumpectomy (often undetected on imaging)
- Sentinel lymph node biopsy is completed with this operation, even with DCIS.

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### How is the sentinel lymph node identified?

- Preoperative injection in the breast center with Technium-99 (radiotracer).
  - Injected at the nipple. Use of intraop instrument that detects this tracer uptake in the patient's lymph nodes.
- Intraoperative injection of lymphazurin (blue dye)
  - Injected at the nipple. Look for blue dye.
  - Urine may be blue or green post op for a day or so.
- Nodes with certain percent of radiotracer activity and/or any blue nodes and/or any hard, palpable nodes are removed. The number removed depends on what is seen/heard/felt during surgery.

Sentinel lymph node biopsy for breast cancer

Sentinel lymph nodes are the first nodes to which cancer cells may spread from a tumor. Sentinel nodes are in the axilla (armpit) and can be identified by a sentinel lymph node biopsy.

- Colored dye and/or radiotracer is injected into breast tissue surrounding the tumor.
- The injected substance drains into the sentinel lymph nodes and identifies them for surgical removal.
- Sentinel lymph nodes are surgically removed and examined for cancer cells.

Information about cancer cells found in the sentinel lymph nodes is used for prognosis and further decisions about breast cancer treatment.

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### Axillary Dissection Anatomy

Figure 1. Anatomical Landmarks of the Axilla and Lymphatic Drainage of the Breast

Published in JAMA 2019  
Axillary node interventions in breast cancer: a systematic review.  
R. Rao, D. Schul, P. Shah, C. Booth

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### Radiation Therapy

- Recommended after majority of lumpectomies. Reduces the risk of a cancer recurrence by approximately 70%
  - Sometimes omitted in women over age 70 with low stage favorable tumors. Especially if negative lymph nodes.
- Recommend after mastectomy when there is residual tumor after neoadjuvant chemotherapy, large tumor size, skeletal muscle or skin invasion, inflammatory breast cancer or positive lymph nodes.
- Recommended for positive axillary nodes vs. axillary dissection. (Z11)
- Can be used for palliative purposes with metastatic disease
- Typical schedule is 5 days a week for 3-7 weeks depending on size of dose. New advances lately with partial breast radiation.

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### Systemic Treatment Options

'70-'80: Morphology, Biochemistry (ER status (protein))

'80-'90: ER/PR/HER2 status (protein), HER2 status (DNA)

2000: Gene expression (RNA), Copy number aberrations (DNA)

2012: Next generation sequencing (DNA), Tumor genomic landscape

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### Chemotherapy

- Oncotype DX:
  - Test of multiple breast cancer biomarkers that combine as a predicted risk of recurrence
  - Used in early stage HR(+) breast cancer
  - Low recurrence score predicts no/minimal absolute benefit of chemotherapy plus endocrine therapy versus endocrine therapy alone
- Neoadjuvant:
  - treatment delivered before surgery for certain types of more aggressive tumors or to try to shrink tumor (patient may then be able to choose lumpectomy over mastectomy) or help convert positive lymph nodes to negative (thus avoid axillary dissection)
- Adjuvant:
  - treatment after surgery

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### Chemotherapy

- Chemotherapy affects cells primarily during cell division in cell cycle.
- Not selective for cell types
- Multiple chemotherapy agents
  - Commonly used: Adriamycin, Cytoxan, Carboplatin, Taxol, Taxotere



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### Chemotherapy

Stages I & II

- Early breast cancer
- Oncotype DX for (HR+) cases
- Treated with combination of chemotherapy, targeted therapy, and endocrine therapy
- One or more of these treatments may be omitted depending on patient age, cancer biology, and other patient related factors

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### Chemotherapy

Stage III

- Locally advanced cancer
- Neoadjuvant treatment with chemotherapy and targeted therapy followed by adjuvant targeted therapy and endocrine therapy for HER2(+) and/or (HR+)
- If not treated prior to surgery then adjuvant treatment with combination of chemotherapy, targeted therapy, and endocrine therapy

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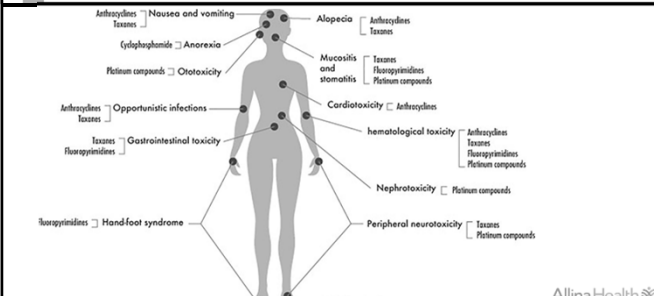
### Chemotherapy

Stage IV

- Chemotherapy for large tumor burden or triple negative breast cancer
- Combination of endocrine therapy plus targeted therapy generally first line therapy for HR(+) cancer
- Balance between control of cancer and quality of life
- Immunotherapy recently approved


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### Chemotherapy



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### Signaling pathways for cancer



Describes a series of chemical reactions in which a group of molecules in a cell work together to control a cell function, such as cell division or cell death.

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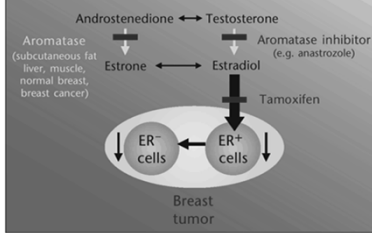
### Targeted therapy for HER2 (+)

- Monoclonal antibodies
  - trastuzumab / biosimilars, pertuzumab, margetuximab; IV or subcut
  - cardiac toxicity (CHF) usually reversible after discontinuing agent
- Antibody-drug conjugates
  - ado-trastuzumab emtansine, fam-trastuzumab deruxtecan; IV
  - cardiac toxicity – reversible
  - diarrhea, can be severe
  - fam-trastuzumab → pulmonary toxicity; can be life-threatening
- Kinase inhibitors
  - lapatinib, neratinib, tucatinib; oral
  - diarrhea, can be severe
  - hand-foot syndrome

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### Targeted therapy - endocrine therapy

- Prescribed for HR+
  - Typically is the last in line of adjuvant treatment
  - Common early use in metastatic setting
  - Oral route
  - Taken for 5 to 10 yrs adjuvant
  - SERMS
    - Primarily premenopausal use
    - Blocks the hormone receptor sites on the cell surface
  - Aromatase Inhibitors
    - Postmenopausal use
    - Blocks the conversion of androgen into estrogen



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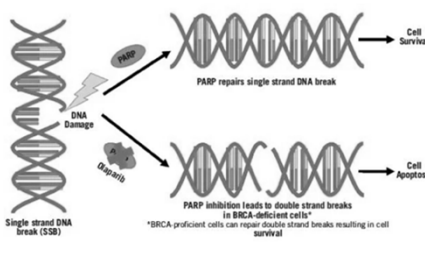
### Targeted therapy for metastatic HR (+)

- Cyclin-dependent kinase - CDK4/6 Inhibitors
  - blocks CDK proteins in the cell to decrease cell division
  - palbociclib, ribociclib, abemaciclib; oral
  - given with endocrine therapy
  - neutropenia; rarely febrile
  - interstitial lung disease / pneumonitis; rare but can be life-threatening
- mTOR inhibitor
  - blocks mTOR, a protein that normally helps cells grow/divide and develop new blood vessels
  - everolimus given with endocrine therapy; oral
- PI3K inhibitor
  - 30-40% of breast cancers have mutated PI3KCA gene
  - blocks a form of the PI3K protein in cancer cells, arresting growth
  - alpelisib; oral
  - given with endocrine therapy
  - HYPERGLYCEMIA,

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### Targeted therapy for BRCA gene mutations

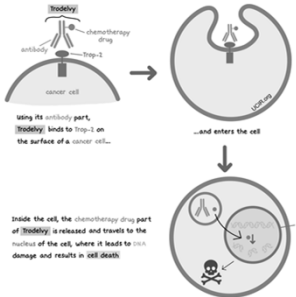
- PARP inhibitor
  - PARP proteins help repair damaged DNA.
  - BRCA genes also help repair damaged DNA but mutations can stop this from happening.
  - mutated BRCA + PARP inhibitor increases odds of cell death
  - olaparib, talazoparib; oral
  - low blood counts, N/V, fatigue
  - risk for developing myelodysplastic syndrome or acute myeloid leukemia



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### Targeted therapy for triple negative

- Antibody-drug conjugate
  - attaches to Trop-2 protein on breast cancer cells and brings chemo (topoisomerase inhibitor) directly cell
  - sacituzumab govitecan; IV



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### Immunotherapy

- Checkpoint inhibitor
  - pembrolizumab – PD-1 inhibitor
- Adjuvant and metastatic triple negative breast cancer
- Expect more approvals for other immunotherapy agents already in use for other types of cancer

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

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### Immunotherapy – Adverse Effects

- Any “itis”
- Common
  - skin, thyroid, GI, joint
- Potentially life-threatening
  - Pneumonitis
  - Colitis
  - Myocarditis
- Treatment
  - hold treatment
  - high dose steroids
  - infliximab / vedolizumab

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### Future of systemic treatment

Microenvironment Modifiers (Indirect): GM-CSF, GTR, Cyclophosphamide, anti-CTLA-4, Treg, Microbiome, Vasculature

Tumor Modifiers (Direct): Chemotherapy, Radiation, Targeted Therapy, Epigenetic Agents

Combination of targeted and immunotherapies based on biology of breast cancer

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### Lymphedema Risk

- Sentinel lymph node
  - Generally low risk if less than 5 nodes removed
  - 5-17% risk
- Axillary dissection
  - 30-40% risk
- Radiation
  - 30-40%
- Other risk factors:
  - Being overweight/obese
  - Injury/infection
  - Over-activity
- Any patient with lymph node removal is referred to Courage Kenny to meet with either a lymphedema therapist or Physical Medicine Rehab (PMR) Provider for education and prevention information and treatment as needed.

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### Survivorship (Thriving after Breast Cancer)

- A person is defined as a survivor from the moment they are diagnosed
- Everybody’s survivorship journey is different
- Goal is to optimize health and wellbeing of a patient both as they go through treatment and afterwards.
  - Physical health
  - Mental health
  - Sexual health
  - Financial health
  - Psychosocial Health

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### Survivorship – NCCN guidelines v3.2021

Exam	H&P 1 – 4 X / year x 5+ yrs
Genetic screening	Periodic review of family history
Post-surgical management	Educate / monitor / refer for lymphedema
Imaging	<ul style="list-style-type: none"> <li>• Mammogram q 12 month unless mastectomy.</li> <li>• Routine screening of reconstructed breast not indicated</li> <li>• Echocardiogram as clinically indicated if received anthracycline-based therapy (Adriamycin).</li> </ul>
Screening for metastases	No indication for laboratory of imaging studies for metastases screening
Endocrine therapy	<ul style="list-style-type: none"> <li>• Tamoxifen → annual GYN exam if uterus present</li> <li>• Aromatase inhibitor → periodic bone density</li> </ul>

Survivorship – NCCN guidelines v3.2021	
Lifestyle	<ul style="list-style-type: none"> <li>• Target of 150 – 300 minutes of moderate physical activity per week</li> <li>• Healthy diet: Fruits, vegetables, whole grains, tree nuts, limit red meats and processed foods.</li> <li>• Ideal body weight (BMI 20-25).</li> <li>• Current ACS guidelines → 1 standard drink daily for both male &amp; female</li> <li>• Smoking Cessation</li> <li>• Sunscreen</li> </ul>
Age Appropriate Cancer Screenings	<ul style="list-style-type: none"> <li>• Mammogram</li> <li>• CRC Screening → new guideline – age 45.</li> <li>• LDCT Lung Cancer Screening → ages 50-80 yrs; 20 pk yr use; current smoker or quit within 15 years</li> <li>• Skin Exam</li> <li>• Management of chronic health conditions to reduce risk for further injury/dysfunction of other body systems. Cardiovascular, DM, Neuropathy, Renal.</li> </ul>

Survivorship – NCCN guidelines v3.2021	
Communication	Coordination of care between primary care provider and specialists
Management of Chronic Health Conditions	To reduce risk for further injury / dysfunction of other body systems; i.e. cardiovascular, DM, neuropathy, renal, etc.

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References
<ul style="list-style-type: none"> <li>• National Comprehensive Cancer Network (NCCN) Guidelines – <a href="http://www.nccn.org">www.nccn.org</a></li> <li>• American Cancer Society – <a href="http://www.cancer.org/cancer/breast-cancer/about.html">www.cancer.org/cancer/breast-cancer/about.html</a></li> <li>• National Cancer Institute – <a href="http://www.cancer.gov/types/breast/hp">www.cancer.gov/types/breast/hp</a></li> <li>• National Lymphedema Network – <a href="https://lymphnet.org">https://lymphnet.org</a></li> <li>• Giuliano, A et al. (2010). ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2N0M0 breast cancer who have a positive sentinel node.</li> <li>• Giuliano, A. et al. (2016). Ten year survival results of ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinic T1-2N0M0 breast cancer who have a positive sentinel node (Alliance). Journal of Clinical Oncology 35:15_suppl, 1007-1007</li> </ul>

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