Breast Cancer

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Purpose The purpose of this course is to explain breast cancer, including diagnostic procedures, types of breast cancer, hormone receptors, mutations, staging, treatment and surgical options, and post-operative complications.

Goals Upon completion of this course, the healthcare provider should be able to:

- Describe the normal breast anatomy.
- Discuss at list 6 risk factors for breast cancer.
- Discuss physical indications of breast cancer.
- Explain the role of mammography, MRI, and ultrasound in diagnosing breast cancer.
- Explain 5 methods of obtaining breast tissue biopsies.
- Discuss the 9 primary types of breast cancer.
- Discuss 3 rare types of breast cancer.
- Explain implications of estrogen-positive and androgen-positive receptors.
- Discuss 5 types of mutations: BRCA1, BRCA2, CEP17, CHEK2/TP53, and HER2.
- Discuss male breast cancer.
- Explain the TNM tumor staging for breast cancer.
- Discuss stage grouping to classify tumors on a 0 to IV scale.
- Discuss 6 methods by which cancer spreads.
- Discuss chemotherapy options, including commonly used drugs and regimens.
- List 4 drugs used as antiestrogens for ER+/PR+ cancer.
- List 2 monoclonal antibodies used as HER2 targeted therapy.
- Discuss use of radiotherapy.
- Differentiate between axillary lymph node dissection (ALND) and sentinel lymph node dissection (SLND).
- Discuss breast conservation surgery.

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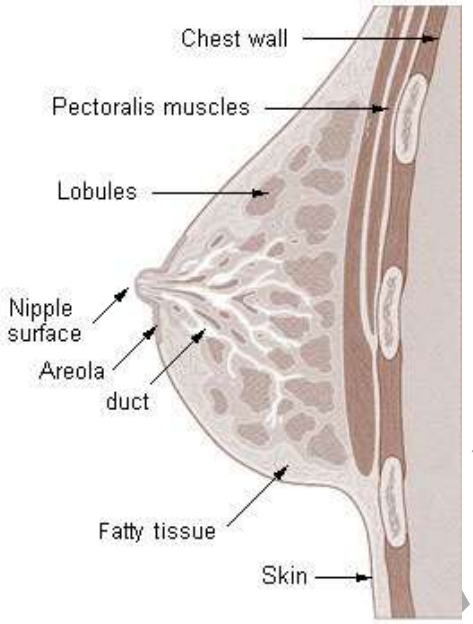
- Discuss 6 types of mastectomies.
- Discuss postoperative care, including pain management, seroma, hematoma, and infection.
- Discuss methods to prevent lymphedema.
- Discuss issues related to depression and impaired body image.

Introduction



Breast cancer remains one of the most common malignancies, affecting more than 200,000 women annually as well as approximately 1700 men. About 80% of cases of breast cancer occur in those >50, so age and female gender are primary risk factors.

Risk factors appear to be cumulative, so the presence of multiple risk factors greatly increases the overall risk of developing breast cancer. Other risk factors include:

- Personal or family history of breast cancer.
- Early menarche or late menopause.
- Nulliparity or first child >30.
- History of hormone therapy.
- History of benign proliferative breast disease.
- Exposure to ionizing radiation during adolescence or early adulthood.
- Obesity.
- Genetic mutations of BRCA-1 or BRCA-2.
- History of alcohol intake.

Early detection is critical as 95% of those diagnosed with early state localized breast cancer have 5-year survival rates but only 21% of those with advanced disease and metastasis.

While Caucasians have the highest incidence of breast cancer, African American women have lower survival rates, even if diagnosed at an earlier stage. Breast cancer is the most common malignancy in

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Hispanic women, and the tumors tend to be larger, more advanced, and diagnosed at a later stage.

Asians have the lowest rates of breast cancer, but statistics vary according to the specific ethnic group. US born Asians have breast cancer rates twice that of foreign-born Asians, but the reasons for the difference are not clear. US born Chinese and Filipina women also tend to have earlier onset of disease and higher rates than Caucasians.

Diagnostic procedures

Physical examination

In some cases, masses may be felt on physical examination or changes may be observed in the breast. The American Cancer Society recommends clinical breast exams every 3 years for women in their 20s and 30s and annually beginning at age 40, when risk increases.

Women should also consider doing routine breast self-exams (BSE) in their 20s and should note the how their breasts look and feel so they can report changes to their physician. However, BSE has not proven very effective in finding breast cancers, but learning the technique can make women more aware of changes to report.

BSE includes observing the breasts in a mirror with the arms in different positions to determine if they are of equal size and configuration. The nipples should be examined for size, shape, and signs of discharge. Palpations should be done with small dime-sized circular movements of the three middle fingers, using first light, then medium, and then firm pressure, moving in a vertical (up and down) pattern from the underarm to the midline of the chest so that the entire breast is covered.

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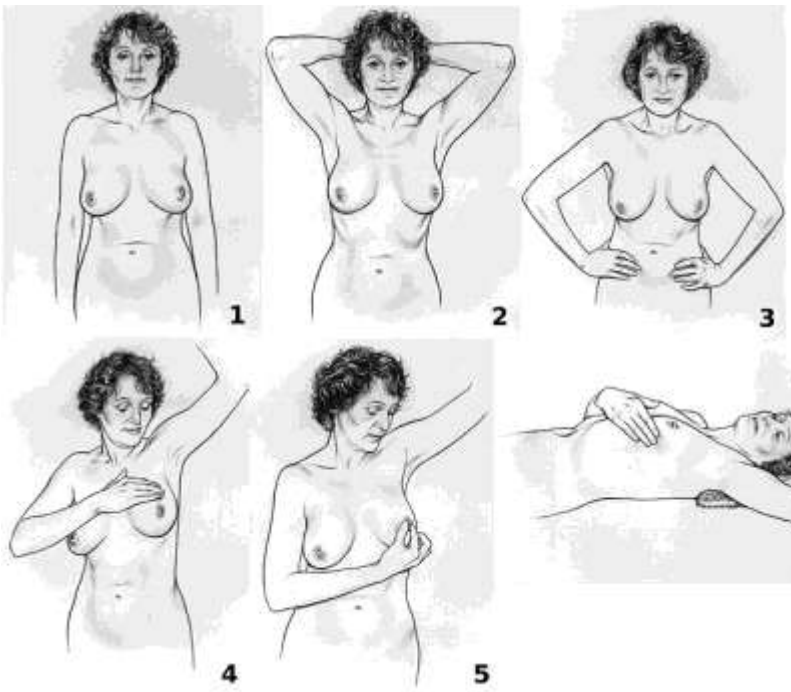
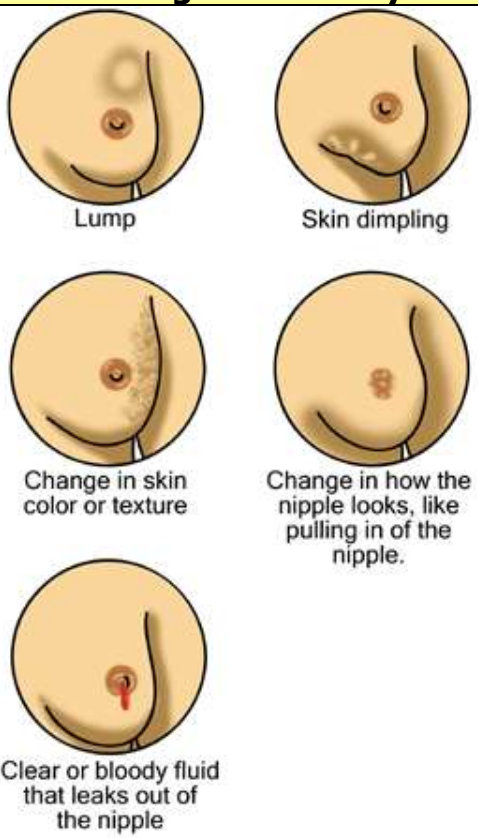
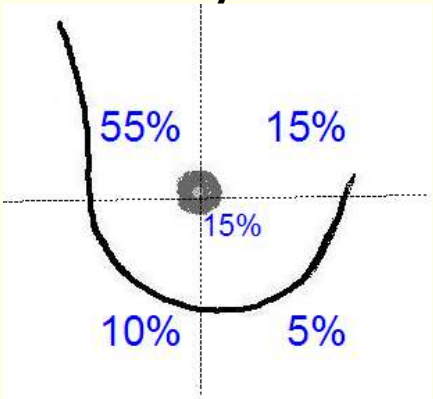


Breast changes that may indicate breast cancer



Change in nipple:

Incidence by location:



Mammogram

The mammogram is recommended for routine screening for women ≥40 years every one to 2 years, continuing as long as they are in good health. It is relatively inexpensive.

Mammograms involve some radiation exposure and may result in false negatives and false positives. Mammograms are less effective in dense breast tissue, so they have limited effectiveness in women <40.

MRI

The MRI is more effective in diagnosing breast cancer than the mammogram, but it is far more expensive, so MRIs are not recommended for routine screening for those with <15% lifetime risk of developing breast cancer. MRI should be done:

- Annually in addition to mammogram for women with >20% risk of lifetime development of breast cancer.
- Considered for women with 15-20% risk of lifetime development of breast cancer.

One problem with MRI is that it identifies more breast lesions but has low specificity; that is, MRI does not effectively distinguish between benign and malignant lesions, so women screened with MRI may undergo unnecessary biopsies. Some studies indicate that a second-look ultrasound exam may help to distinguish benign from malignant lesions found on MRI.

Recent research (2011) at the University of Washington and Seattle Cancer Care Alliance involving 570 breast cancer patients reported that the use of preoperative breast MRI in newly diagnosed breast cancer patients found an extra cancer yield of 12% because the MRI was able to detect otherwise occult cancer.

A similar study (2009) of preoperative MRI at Dartmouth Hitchcock Medical Center involved 199 patients and found additional cancer in

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the same breast in 16% of patients and cancer in the opposite breast in 4% of patients.

Ultrasound

Standard ultrasound is often used as an adjunct to mammography to determine if a lesion is solid or fluid-filled and to detect other abnormalities of tissue. Ultrasound may provide better results than mammography for dense breasts or those with very small breasts or silicone implants. It can also be used with pregnant women. However, as a screening tool, ultrasound also has low specificity and may identify benign lesions. Ultrasound is often used to guide biopsy procedures.

A new technique using high-frequency ultrasound with elastography can help differentiate benign from malignant tumors with good accuracy. This technique indicates tissue softness. Malignant tissues are harder than benign. One study found that ultrasound with elastography was able to correctly identify 79% of 115 lesions as malignant. This ultrasound may also be used for those who cannot tolerate contrast-enhanced MRI.

CT scan/ x-rays

CT scans and x-rays are not routinely used to diagnose breast cancer, but they may be ordered at times to determine if the cancer has invaded the chest wall or other parts of the body. CT scans are not usually indicated in early stage cancer. Research is ongoing to determine if CT breast scanning may be a better screening tool than mammography as the radiation is approximately the same; however, CT scans are more expensive.

Fine-needle aspiration

Fine-needle aspiration (FNA) involves aspirating a small amount of a lesion in order to examine the cells microscopically to determine if the lesion is malignant.

FNA is usually done in the physician's office and takes only a few minutes. A local anesthetic may be administered prior to the procedure. Results are usually available within 2 to 3 days.

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Needle (wire) localization biopsy

With needle (wire) localization biopsy, the position of the lesion is verified with mammogram, and then (under local anesthetic) a needle with a small wire attached is inserted into the breast with the tip of the needle at the lesion and the wire taped to the skin to secure it. The placement is again checked with mammogram.

With the needle and wire in place and pinpointing the lesion, the patient is taken into surgery and an excisional biopsy done, using the wire and needle as a guide.

Stereotactic core biopsy

Stereotactic core biopsy is an alternative to standard surgical biopsy, requiring a procedure similar to a mammogram except that the patient is lying face down while the breast is compressed between paddles. An x-ray is taken to ensure the lesion is correctly positioned between the paddles and then to stereo x-rays are taken from different perspectives.

A computer then determines the exact position needed for a biopsy needle. Under a local anesthetic, the physician then inserts the biopsy needle into the lesion. Once the correct position is confirmed by x-ray, a sample is aspirated.

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Open surgical biopsy

Open surgical biopsies may be done in the doctor's office or as an outpatient, depending on the size and location of the lesion. Most surgical biopsies are done under local anesthesia with or without conscious sedation. A small sample of tissue is excised.

The size of the incision varies, but is usually 2.5 to 5 cm. If a lesion is small (≤2.5 cm), usually the entire lesion is removed during the biopsy. If the lesion is large, only part of it may be removed, or if the lesion is cancerous, a lumpectomy may be performed if the patient has given consent.

While non-invasive biopsies are less stressful and leave little or no scarring, they are not always as reliable, so sometimes patients who undergo a non-invasive biopsy may then need confirmation with a surgical biopsy.

Vacuum-assisted biopsy

Vacuum-assisted biopsy uses a special instrument and imaging guidance to place a biopsy probe to identify the area to be biopsied. Once imaging (multiple mammograms, MRI, ultrasound) has confirmed placement, breast tissue is suctioned into the probe into a sampling chamber and a rotating cutting device removes a tissue sample.

Sampling may be repeated multiple times during the procedure to take different tissue samples. Vacuum-assisted biopsy requires only a small skin incision but allows for removal of more tissue than a stereotactic core biopsy or FNA and is usually less invasive than a standard surgical biopsy.

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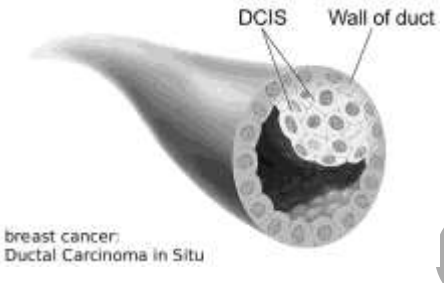
Types of breast cancer

Breast cancer may be classified according to location and histology. Carcinoma is a cancer originating in epithelial (lining) cells. Adenocarcinoma refers to cancer originating in glandular tissue, so most breast cancers are both carcinomas and adenocarcinomas. On rare occasions, sarcomas, cancer of connective tissue (muscles, blood vessels, fat), can occur in the breast. There are many types of breast cancer, and some have a mixed type, such as both invasive ductal and lobular carcinoma. Cancer that spreads may be referred to as infiltrating or invasive.

Ductal carcinoma in situ (DCIS)

DCIS is the most common noninvasive breast cancer, accounting for 20%, also sometimes referred to as intraductal carcinoma in situ. Malignant cells proliferate

in the milk ducts but do not invade surrounding tissues although if not diagnosed early, it may progress to an invasive form of cancer.



Areas of dead or dying cancer cells (tumor necrosis) represent a more aggressive tumor.

Infiltrating ductal carcinoma Infiltrating ductal carcinoma accounts for 75-80% of invasive breast cancers with tumors arising from ductal system and invading surrounding tissue, often forming a solid irregular-shaped mass.

NOTE: **Triple-negative breast cancers** are almost always infiltrating ductal carcinomas. These tumor cells lack estrogen and progesterone receptors as well as excess HER2 protein [see below], so hormone therapy and Herceptin® are not effective. These tumors tend to grow and metastasize rapidly because targeted therapy is not available. Risk factors include obesity combined with lack of physical activity.

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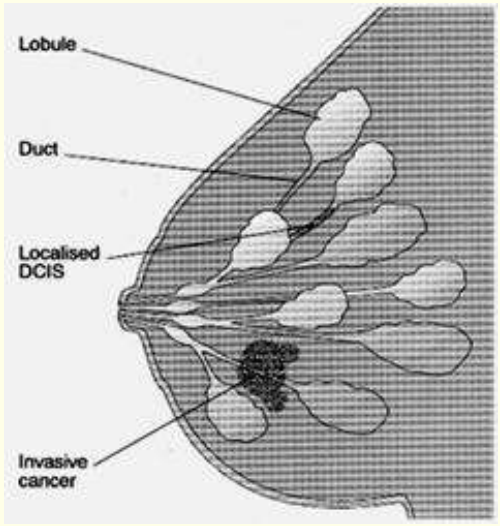

Infiltrating lobular carcinoma

Infiltrating lobular carcinoma accounts for 5-10% of invasive breast cancers with tumors arising from the lobular epithelium. Tumor may appear as an ill-defined thickening of the breast tissue. Tumors are often multicentric and may occur bilaterally.

NOTE: Lobular neoplasia is sometimes referred to as **lobular carcinoma in situ** (LCIS) although it is not a true malignancy. It begins in the milk glands but does not infiltrate. However, women with this abnormality are at increased risk of breast cancer developing in the same or opposite breast.

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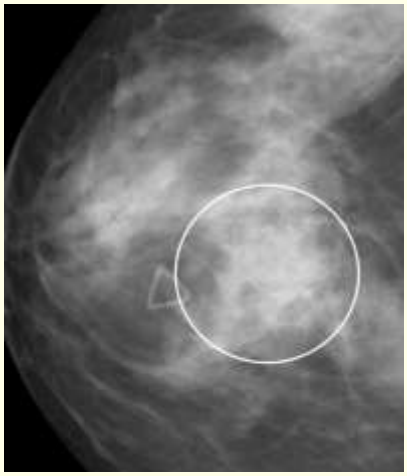

Inflammatory carcinoma

Inflammatory carcinoma accounts for 1-2% of invasive breast cancers and is an aggressive cancer characterized by diffuse erythema and edema of skin (peau d'orange), resembling an orange peel. The characteristic appearance results from blockage of lymph channels by malignant cells.

The cancer may cause a large thickened area with or without an associated mass. Without mass, it may be difficult to diagnose with mammography. Inflammatory carcinoma may be misdiagnosed as an infection and initially treated with antibiotics. If antibiotics are not successful, breast cancer should be suspected. Inflammatory carcinoma metastasizes rapidly.

Paget's disease of the nipple

Paget's disease of the breast/nipple accounts for about 1% of invasive breast cancers and is characterized by scaly, erythematous, pruritic lesion of the nipple. The tumor usually starts with the ducts and spreads to the nipple and areola Paget's disease usually is a form of ductal carcinoma in situ of the nipple although it may become invasive. Paget's disease is almost always associated with DCIS or infiltrating ductal carcinoma.

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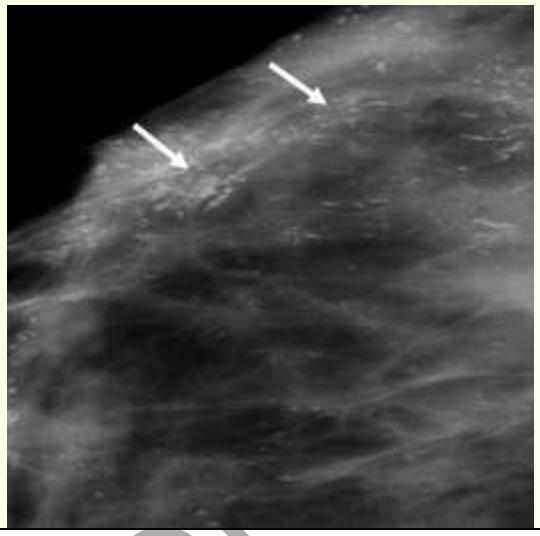

Medullary carcinoma Medullary carcinoma accounts for about 3-5% of invasive breast cancer and is usually diagnosed in females <50, so it is an early onset cancer.

The tumors are encapsulated and well defined inside a duct and can become quite large. They may be misdiagnosed as fibroadenoma. Prognosis is good. Invasive ductal carcinoma may be misdiagnosed as medullary carcinoma.

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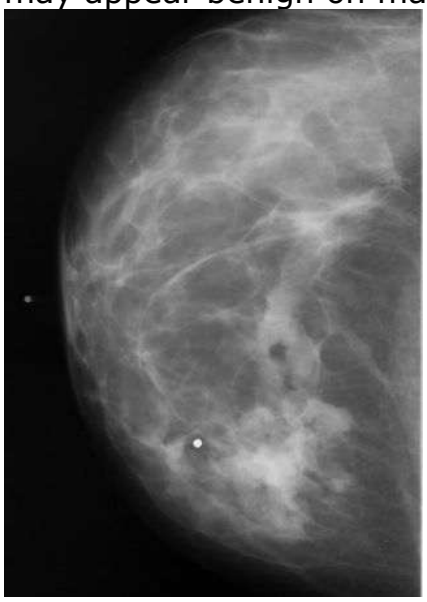
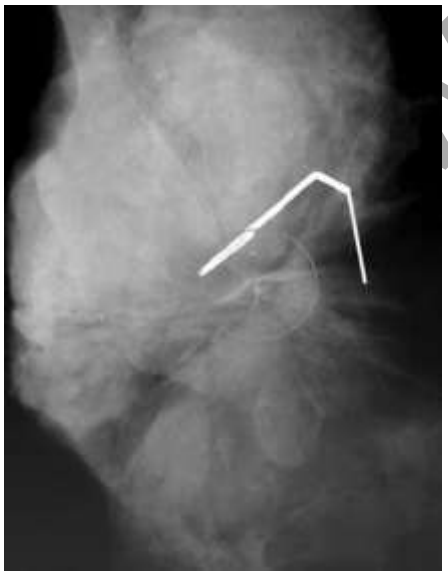
Mucinous/Colloid carcinoma Mucinous/Colloid carcinoma, a rare tumor, is formed by mucus producing cells and accounts for about 3% of cancers. The cancer cells are encased in pools of mucin. Mucinous carcinoma is most common in postmenopausal women >75. This is a slow-growing tumor that rarely spreads to the lymph nodes, so prognosis is good. Tumors usually range in size from 1 to 5 cm and

have well-defined edges, so the tumor may be palpable. This tumor may appear benign on mammogram.



Tubular ductal carcinoma

Tubular ductal carcinoma accounts for about 2% of breast cancers and are a subtype of infiltrating ductal carcinoma



The cells have a tubular appearance when viewed microscopically. Prognosis is better than many other types.

Adenoid cystic (adenocystic) carcinoma

This tumor accounts for <1% of breast cancers and contain both glandular (adenoid) and cystic (cylinder-like) features. The tumor rarely metastasizes,

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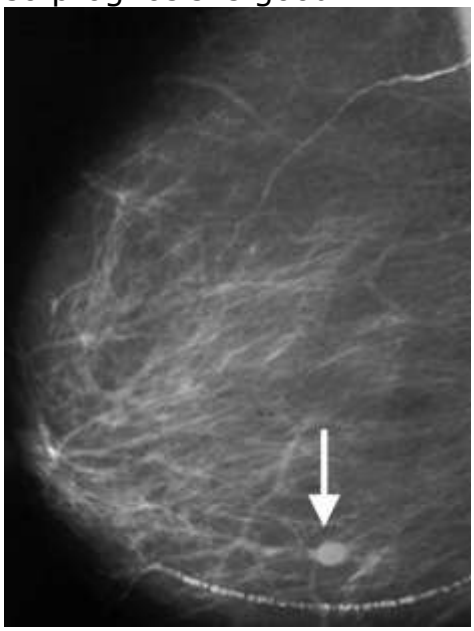
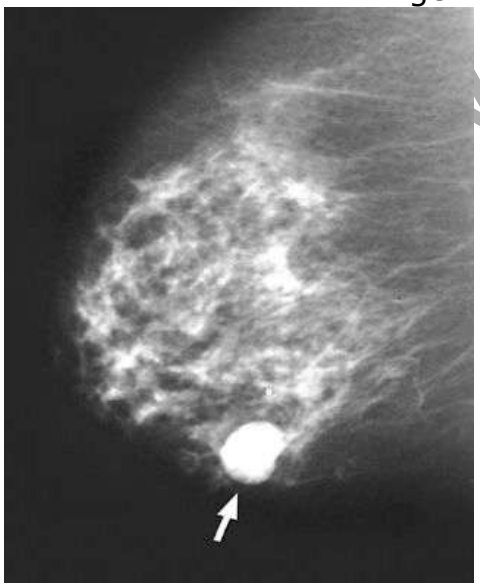
so prognosis is good.



Papillary carcinoma

Papillary carcinoma accounts for 1-2% of breast cancers and is characterized by tumor with finger-like projections.



Papillary carcinoma may be invasive or noninvasive, and the noninvasive form is often considered a subtype of DCIS and treated similarly.

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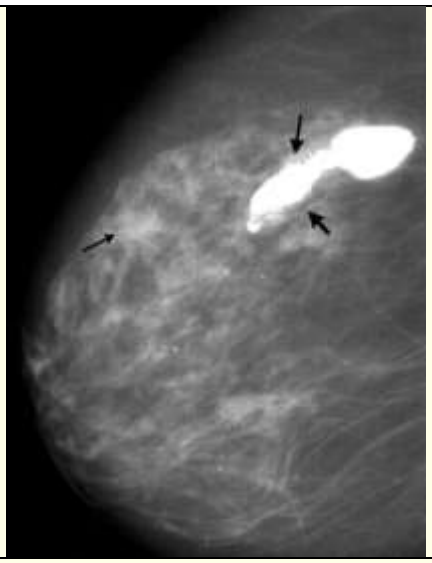
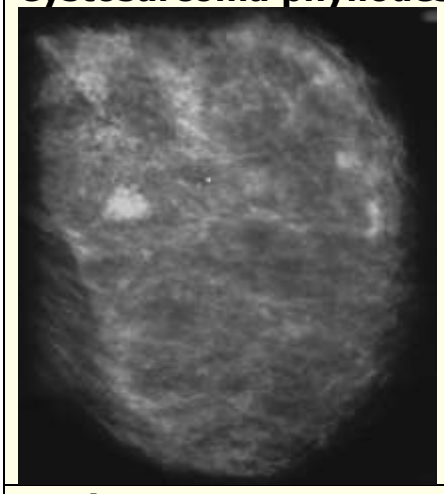
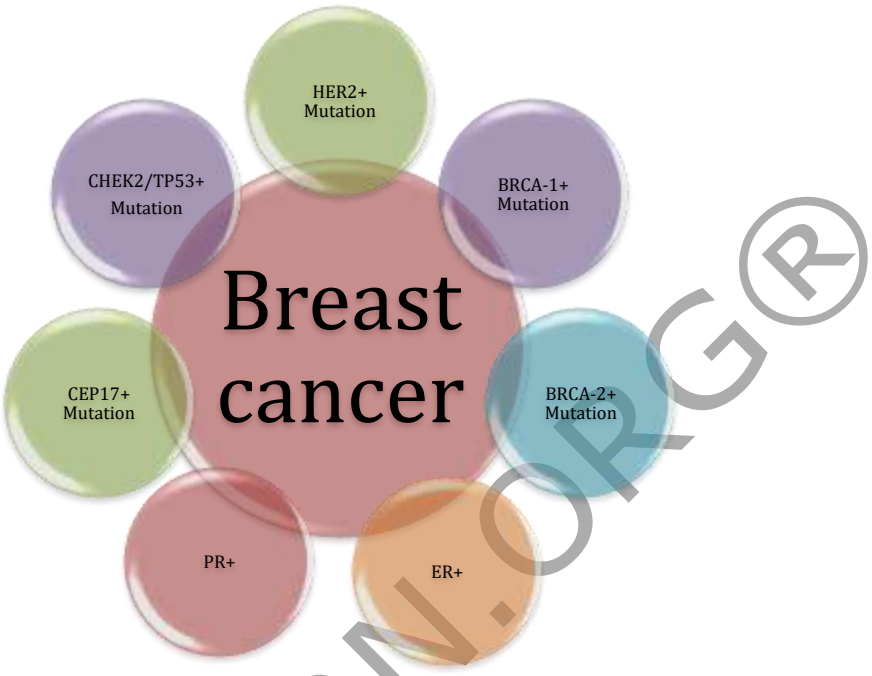
Rare tumors	
Metaplastic carcinoma	Very rare ductal cancer that contains

	cells not normally found in the breast, such as squamous-like cells or osteocytes.
Cystosarcoma phyllodes 	Rare tumor arises in stroma (connective tissue) and is usually benign. Malignant tumors are more resistive to chemotherapy than other types of tumors.
Angiosarcoma 	Rare tumor arises in linings of blood vessels or lymph vessels and is usually a complication of previous radiation, occuring about 10-15 years after treatment.

ER, PR, HER2, and other mutations



The diagnosis of breast cancer is only the first step in determining treatment. Other factors must be considered, including the presence of hormone receptors and mutations, which may affect the growth, treatment, and prognosis of the breast cancer.

Estrogen receptor (ER) and progesterone receptor (PR)

Some breast cancer cells have estrogen receptors and/or progesterone receptors, indicating that the cells respond to hormone levels, but with cancer cells, the hormones essentially feed the cancer and promote growth. Approximately 75% of those with breast cancer test positive for estrogen receptors and 65% of these also test positive for progesterone receptors.

Cancer cells with estrogen receptors are classified as ER-positive and with progesterone receptors PR-positive. If no receptors are present, they are classified as ER-negative and/or PR-negative. Cancer cells are routinely tested for hormone receptors to determine if drugs that lower the hormone level will decrease tumor growth.

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Drug therapy for ER-positive and/or PR-positive cancers includes Selective estrogen-receptor response modulators (SERMs), such as tamoxifen, which block the effects of estrogen or aromatase inhibitors, such as anastrozole (Arimidex® and letrozole (Femara®), which stop estrogen production in post-menopausal women. Those who test ER+ are 60% likely to respond to hormone treatment.

Other treatments that may be used if the first-line drugs are ineffective include estrogen-receptor downregulators (ERDs), which block the effects of estrogen, and luteinizing hormone-releasing hormone agents (LHRHs), which stop the ovaries from producing estrogen.

HER2 mutation

The HER2 gene is responsible for production of HER2 protein, which has an important role in cell growth and development. Growth factors attach to the HER2 receptors and signal cell growth.

About 20 to 25% of breast cancers test positive for overexpression of human epidermal growth factor receptor 2 (HER2), resulting in increased growth factor receptor protein on the tumor cell; that is, the cells produce too much of a protein because of a gene mutation, so the cancer cells begin to grow, divide, and multiply more rapidly than normal. The tumors tend to be more aggressive than those without the mutation with increased risk of recurrence.

These tumors are less responsive to hormone-blocking medications, but can be treated with monoclonal antibody drugs that suppress HER2, such as trastuzumab (Herceptin®) and Lapatinib (Tykerb®) as well as other chemotherapeutic agents.

Mutations may occur after initial treatment of breast cancer, so if a patient has recurrence, the cancer cells should be retested for HER2. This change occurs in 20-30% of cases.

CHEK2 and TP53 mutations

Li-Fraumeni syndrome is a rare autosomal dominant genetic disorder that results in mutations in either the CHEK2 or TP53 (most common) gene. These are tumor suppressor genes that normally control growth and division of cells, but the mutations allow cells to divide uncontrollably and form tumors. Children and young adults are at risk for developing a number of different types of tumors, with

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especially high rates of breast cancer, osteosarcoma, brain tumors, acute leukemia, and soft tissue sarcomas.

Those with Li-Fraumeni syndrome have a lifetime risk of cancer of 85% with half of tumors before age 30. Patients presenting at a young age with breast cancer and with other risk factors should be evaluated for Li-Fraumeni syndrome to help predict future risks.

While some authorities recommend early regular mammogram screenings for those with Li-Fraumeni syndrome, others suggest that the breast density of younger females makes the mammogram unreliable. MRI screening may be more effective. At present, there is no specific targeted treatment for breast cancer in those with Li-Fraumeni syndrome, so the cancers are treated according to standard protocols.

BRCA1 and BRCA2 mutations

Approximately 5 to 10% of breast cancer patients inherited a genetic abnormality that increased their risk of developing breast cancer. The BRCA1 gene, located on chromosome 17, is a tumor suppressor gene when functioning normally, but those with a mutation of this gene have a 50-85% lifetime risk of developing breast cancer. Most breast cancers associated with the BRCA1 mutation are triple negative, making commonly-used treatments, such as tamoxifen and Herceptin®, ineffective.

Another tumor suppressor gene, BRCA2, located on chromosome 11, also increases risk of breast cancer similarly to BRCA1 in those with mutations. Both BRCA1 and BRCA2 are associated with early-onset breast cancer. These women are also at increased risk of ovarian cancer.

Routine screening for genetic mutations is not usually done because of cost, but those with a strong evidence of familial breast cancer should be tested and apprised of risks. There is no targeted treatment for these mutations, but many women may choose to undergo elective bilateral mastectomy and/or bilateral oophorectomy.

CEP17

A duplication abnormality on chromosome 17, CEP17, is associated with worse outcomes but is also predictive of tumor response to anthracyclines. Those who are positive for the CEP17 duplication and treated with anthracyclines are 67% more likely

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to survive without recurrence of cancer than those treated with other agents. A study of 3000 patients with breast cancer indicated that approximately 27.5% showed the CEP17 duplication. The study suggested that those patients without CEP17 duplication may not benefit from anthracyclines.

Male breast cancer
Male breast cancer comprises 1% of the total. Although it can occur at any age, onset is usually between 60 and 70. Risks include history of radiation, estrogen administration, cirrhosis, and Klinefelter syndrome. Mutations, such as BRCA2, also increase risk in males. The most common type of breast cancer is infiltrating ductal carcinoma. Lobular carcinoma in situ has not been found in males but intraductal, inflammatory, and Paget's disease of the nipple have been. Spread to the lymph nodes and metastasis are similar to that in women and the same staging system is used. Survival rates are also similar to women at the same stage, but male breast cancer is often not diagnosed until a later stage.

Tumor staging

The system most commonly used to stage breast cancer is that of the American Joint Committee on Cancer. Tumor (T) staging describes the size of the tumor. Lymph node (N) staging indicates whether cancer cells have spread to the adjacent lymph nodes. Metastasis (M) staging indicates the spread to other organs.

Tumor	**Node**	**Metastasis**
TX: Primary tumor cannot be assessed. **T0**: No evidence of primary tumor. **Tis**: Carcinoma in situ (DCIS, LCIS, or Paget disease of the	**NX:** Nearby lymph nodes cannot be assessed (for example, removed previously). **N0:** Cancer has not spread to nearby lymph nodes although tiny amounts may be found with special stains (i+) or PCR (mol+). **N1**: Cancer has spread to 1 to 3 axillary (underarm) lymph node(s), and/or tiny amounts of cancer are found in internal	**MX:** Presence of distant spread (metastasis) cannot be assessed. **M0**: No distant spread is found on x-rays (or other imaging procedures) or by physical exam.

nipple with no associated tumor mass) **T1:** Tumor is 2 cm (3/4 of an inch) or less across. **T2:** Tumor is more than 2 cm but not more than 5 cm (2 inches) across. **T3:** Tumor is more than 5 cm across. T4: Tumor of any size growing into the chest wall or skin. This includes inflammatory breast cancer.	mammary lymph nodes (those near the breastbone) on sentinel lymph node biopsy. **N1mi:** Micrometastases (tiny areas of cancer spread) in 1 to 3 lymph nodes under the arm. The areas of cancer spread in the lymph nodes are 2 mm or less across (but at least 200 cancer cells or 0.2mm across). **N1a**: Cancer has spread to 1 to 3 lymph nodes under the arm with at least one area of cancer spread greater than 2 mm across. **N1b:** Cancer has spread to internal mammary lymph nodes, but this spread could only be found on sentinel lymph node biopsy (it did not cause the lymph nodes to become enlarged). N1c: Both N1a and N1b apply. **N2**: Cancer has spread to 4 to 9 lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes (either N2a or N2b, but not both). • **N2a:** Cancer has spread to 4 to 9 lymph nodes under the arm, with at least one area of cancer spread larger than 2 mm. • **N2b:** Cancer has spread to one or more internal mammary lymph nodes, causing them to become enlarged. **N3**: Any of the following: • **N3a:** either cancer has spread to 10 or more axillary lymph nodes, with at least one area of cancer spread greater than 2mm, OR cancer has spread to the lymph nodes under the clavicle (collar bone), with at least one area of cancer spread	**cM0(i +):** Small numbers of cancer cells are found in blood or bone marrow (found only by special tests), or tiny areas of cancer spread (no larger than 0.2 mm) are found in lymph nodes away from the breast. **M1:** Spread to distant organs is present. (The most common sites are bone, lung, brain, and liver.)

	greater than 2mm. • **N3b**: either cancer is found in at least one axillary lymph node (with at least one area of cancer spread greater than 2 mm) and has enlarged the internal mammary lymph nodes, OR cancer involves 4 or more axillary lymph nodes (with at least one area of cancer spread greater than 2 mm), and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy. • **N3c:** Cancer has spread to the lymph nodes above the clavicle with at least one area of cancer spread greater than 2mm.	

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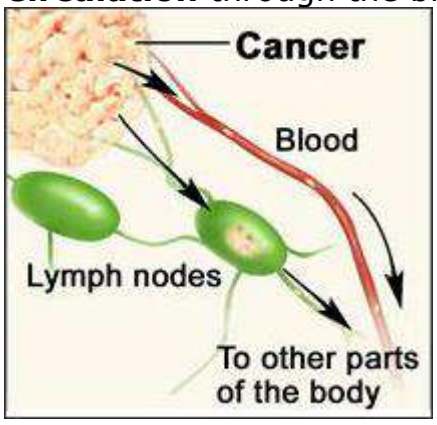
After the initial TNM staging is completed, the findings are combined in stage grouping to classify tumors on a 0 to IV scale

Stage	T	N	M	Description
0	is	0	0	Ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).
IA	1	0	0	Tumor is ≤2 cm across and no spread.
Ib	0-1	1ml	0	Tumor is ≤2 cm across or not found with micrometastases to 1-3 axillary lymph nodes.
IIA	0-1	1	0	Tumor is ≤2 cm across or not found with either: Spread to 1-3 axillary lymph nodes (cancer > 2mm) OR Sentinel node biopsy shows tiny amount of cancer in internal mammary lymph nodes OR Spread to 1-3 axillary lymph nodes and to internal mammary lymph nodes.
IIA (Alternate)	2	0	0	Tumor >2 cm and <5 cm with no spread.
IIB	2	1	0	Tumor >2 cm and <5 cm with spread to 1-3 axillary lymph nodes and tiny amounts in internal mammary lymph

				nodes.
IIB (Alternate)	3	0	0	Tumor >5 cm but has not grown into chest wall or skin or spread to lymph nodes or distant sites.
IIIA	0-2	2	0	Tumor is ≤5 cm or cannot be found and has spread to 4-9 axillary lymph nodes or has enlarged the internal mammary nodes but no distant spread.
IIIA (Alternate)	3	1-2	0	Tumor is >5 cm but does not grow into chest wall or skin. It has spread to 1-9 axillary nodes or to internal mammary nodes but hasn't spread to distant sites.
IIIB	4	0-2	0	The cancer has spread into the chest wall but no distant sites and one of the following: It has not spread to lymph nodes. It has spread to 1-3 axillary lymph nodes and tiny amount found in internal mammary lymph nodes. It has spread to 4-9 axillary lymph nodes or has enlarged the internal mammary lymph nodes. NOTE: Inflammatory cancer is classified as T4 and staged IIIB unless it has spread to distant lymph nodes or organs, in which it is staged V.
IIIC	Any	3	0	Tumor is any size or can't be found with no distant metastasis and one of the following: It has spread to ≥10 axillary nodes. It has spread to lymph nodes under clavicle. It has spread to lymph nodes above the clavicle. It has spread to ≥4 axillary lymph nodes and tiny amounts found in internal mammary lymph nodes.
IV	Any	Any	1	Tumor is any size with or without spread to nearby lymph nodes but has spread to distant lymph nodes or organs.

Tumor spread

Breast cancer may spread in a variety of ways:

- **Invasion** of local tissue as the tumor grows.
- **Intravasation** through walls of lymph or blood vessels.
- **Circulation** through the bloodstream.
- 

- **Arrest and extravasation** as the cancer cells become blocked (arrested) in capillaries distant from the breast and then invade the walls and spread into adjacent tissue.
- **Proliferation** of cancer cells that have spread to distant sites, creating micrometastases (small tumors).
- **Angiogenesis** as micrometastases stimulate the growth of new vessels to provide nutrients to the growing tumors.

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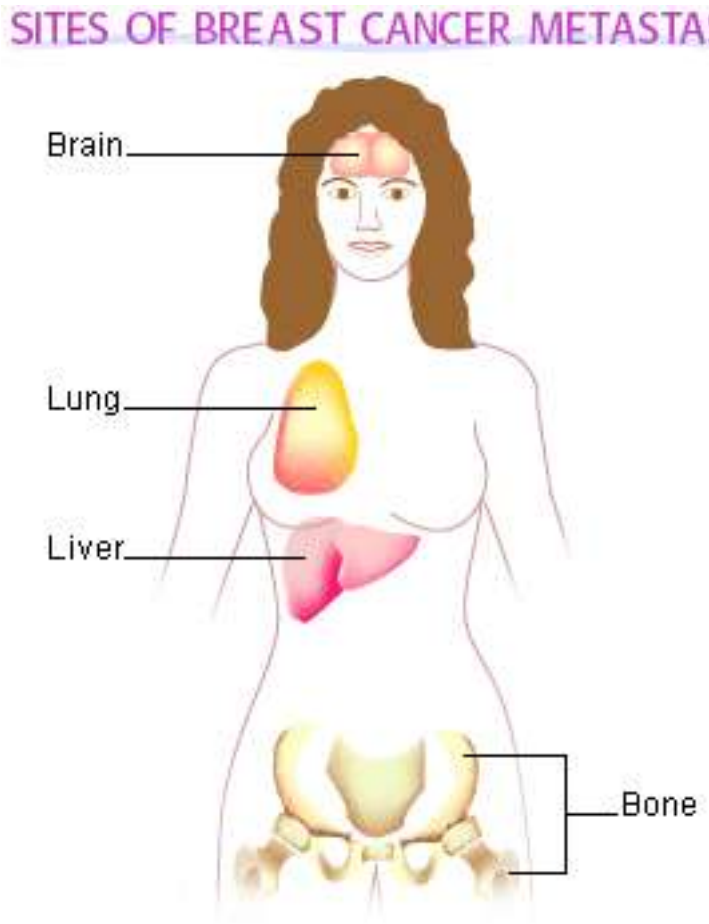

Treatment options

Treatment may include local therapy (surgery and radiation) and adjuvant therapy (chemotherapy, hormone therapy, and/or targeted therapy with monoclonal antibodies) or neoadjuvant therapy, which is given prior to surgery.

Chemotherapy Multiple chemotherapeutic agents are used in the treatment of breast cancer, depending on the stage of the disease and other factors. Agents may include:

- **Anthracyclines:** Doxorubicin (Adriamycin®) and epirubicin (Ellence®).
- **Mitotic spindle poisons (taxanes):** Paclitaxel (Taxol®) and docetaxel (Taxotere®).
- **Alkylating agents:** Cyclophosphamide (Cytoxan®)
- **Antimetabolites:** 5-fluorouracil (5-FU), gemcitabine (Gemzar®, and methotrexate.

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Anthracyclines, also referred to as anthracycline antibiotics, are derived from Streptomyces bacteria. The anthracyclines are some of the most effective chemotherapeutic agents used to treat a variety of cancers, including breast cancer. Anthracyclines interfere with DNA and RNA synthesis and cell duplication. Anthracyclines may, however, result increased risk of heart damage and leukemia and may be associated with severe adverse effects, such as nausea, vomiting, loss of hair, and anorexia.

As noted above, those with the CEP17 mutation may benefit most from anthracyclines. Other research indicates that survival rates of those with HER2 overexpression improve with anthracyclines, but those who are HER2 negative may not have benefit.

Usually some combination of different types of chemotherapeutic agents is used. Commonly used chemotherapeutic regimens include:

- **AT:** Adriamycin® and Taxotere®.
- **AC ± T**: Adriamycin® and Cytoxan® with or without Taxol® or Taxotere®.
- **CMF:** Cytoxan®, methotrexate, and 5-fluorouracil.
- **FAC:** 5-Fluorouracil, Adriamycin®, and Cytoxan®.
- **CAF:** Cytoxan®, Adriamycin®, and 5-fluorouracil (The FAC and CAF regimens use the same medicines but use different doses and frequencies).
- **TAC:** Taxotere®, Adriamycin®, and Cytoxan®.
- **GET:** Gemzar®, Ellence®, and Taxol®.
- **TC:** Taxotere® and Cytoxan®
- **FEC:** 5-fluorouracil, Ellence® and Cytoxan®.
- **FECD:** FEC given 3-weekly for 3 cycles followed by docetaxel given 3-weekly for 3 cycles

The duration of treatment and number of cycles varies, depending on the protocol used and the type and stage of cancer. Most chemotherapeutic agents have severe side effects, which may include bone marrow suppression with leukopenia and thrombocytopenia, putting the person at increased risk for infection and bleeding.

In some cases, such as patients who wish to have breast conserving surgery for tumor >2cm, patients may elect neoadjuvant therapy (chemotherapy, hormone therapy, or targeted therapy) prior to surgery to shrink the tumor.

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Hormone and targeted therapy

Hormone (antiestrogen) and targeted therapy, monoclonal antibodies, such as Herceptin®, may also be used, depending on the characteristics of the tumor.

Hormone and targeted therapies		
Tamoxifen citrate (Nolvadex®) (First-line drug)	• ER+/PR+ cancer. • Risk reduction after surgery. • Metastatic cancer in males in females. • Premenopausal women with metastasis as alternative to oophorectomy or ovarian irradiation.	**Administration**: 20 mg orally daily x 5 years. **Action**: Blocks the effects of estrogen/progesterone by competing for binding sites in premenopausal women. **Adverse effects:** DVT, hot flashes, rash, vaginal bleeding and discharge, pruritus vulvae, milk production, hypercalcemia (with bone metastasis), peripheral edema, increased bone and tumor pain, depression, dizziness, CVA, retinopathy, decreased visual acuity. Headache, lethargy, nausea and vomiting rare.
Anastrozole (Arimidex®)	ER+/PR+ cancer or status unknown.	**Administration**: 1 mg orally daily x 5 years. **Action**: Stops estrogen production in post-menopausal women. **Adverse effects:** Hot flashes, vaginal dryness, mild peripheral edema, mild nausea and vomiting, diarrhea, constipation, arthralgias, skin rash, flu-like symptoms (fever, malaise), decreased energy, and weakness.
Letrozole (Femara®)	• ER+/PR+ cancer. • Advanced breast cancer in post-menopausal women. • Disease	**Administration**: 2.5 mg daily for 5 years usually started after 5 years of tamoxifen. **Action**: Inhibits conversion of androgens to estrogens by the aromatase system in post-menopausal women, reducing levels of estrogen in all tissues.

	progression after other antiestrogen treatment. • Post-surgical adjunct treatment of post-menopausal women with early breast cancer.	**Adverse effects:** Headache, depression, hot flashes, thromboembolic events, nausea, GI upset, cough, dyspnea, chest wall pain, peripheral edema, bone and back pain, anxiety, vertigo, dizziness, and insomnia. Mild constipation or diarrhea.
Exemestane (Aromasin®)	• ER+PR+ cancer. • Advanced breast cancer in those whose disease progresses with tamoxifen. • Post-menopausal women with early breast cancer.	**Administration**: 25 mg orally daily for remainder of 5 years after initial 2-3 years of tamoxifen. **Action**: Inhibits conversion of androgens to estrogens by the aromatase system in post-menopausal women, reducing levels of estrogen in all tissues. **Adverse effects:** Hot flushes, fatigue, arthralgia, insomnia, headache, nausea, increase sweating, joint & musculoskeletal pain. Anorexia, depression, dizziness, carpal tunnel syndrome, GI effects, rash, alopecia, osteoporosis, leg edema, abdominal pain, vomiting, constipation, dyspepsia, and diarrhea.
Trastuzumab (Herceptin®)	• HER2+ cancer. • Risk reduction to prevent recurrence. • Metastatic cancer.	**Administration**: 2m/kg to 8 mg/kg IV, depending on treatment protocol. May be given 1 X weekly if given with other chemotherapeutic agents or every 3 weeks if given after completion of other chemotherapy. Herceptin is usually administered for 1 year. **Action**: Human anticlinal antibody to the HER2 receptor protein.

		Adverse effects: Fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, anemia, leucopenia, and myalgia. NOTE: Severe heart and lung damage may occur.
Lapatinib (Tykerb®)	HER2+ advanced or metastatic disease after treatment with an anthracycline, a taxane, and Herceptin®.	**Administration**: 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine (Xeloda®) 2,000 mg/m2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. **Action:** Tyrosine kinase inhibitor that blocks the effects of the HER2 protein and other proteins inside tumor cells. **Adverse effects:** Dysrhythmia, severe dizziness or fainting, diarrhea, shortness of breath, dry cough, oral moniliasis, nausea, stomach pain, fever, anorexia. **NOTE**: May cause severe life-threatening liver damage.

Radiation therapy

Radiation therapy is often used with breast cancer of all stages. It may also be used for metastatic lesions, such as for painful metastasis to the bone. Radiation is routinely recommended for those who opt for lumpectomy rather than mastectomy if the cancer is early stage, ≤4 cm in size, located in one site, and removed with clear margins.

Radiation may also be recommended after mastectomy if patients are have factors that represent high risk of recurrence:

- Tumor is ≥5 cm total (one or more lesions).
- Invasion of lymph channels and blood vessels in the breast.
- Tissue has positive margin of resection.

- ≥4 lymph nodes involved OR for premenopausal women, at least one lymph node is involved.
- Invasion of skin.
- The risk for recurrence is 20 to 30%. (Radiation therapy reduces this risk by up to 70%.)

Patients with moderate risk factors should discuss all options with their physicians to decide if they might benefit from radiation. External radiation is usually given for 5 to 6 weeks.

High-dose brachytherapy may be used as an alternative to external radiation for early-stage cancer. After tumor removal, a catheter with a deflated balloon is inserted into the cavity created by the surgery. In 1-5 days (or even at the time of surgery) a radioactive seed in inserted into the balloon for 10 minutes. A seed is inserted twice daily for 10 minutes each time to target the area where recurrence is most likely to occur. The treatment is usually complete and the catheter removed in about 5 days.

The sequence of radiation with other treatments varies. It usually follows surgery and chemotherapy and precedes hormonal therapy, but this may vary with individuals. Radiation can be started one month after completing anthracycline chemotherapy and 2-3 weeks after the last dose of a taxane.

With surgery but no chemotherapy, radiotherapy may include:
- External beam started 3-6 weeks after surgery.
- Partial breast radiation immediately after surgery.
- Intraoperative radiation before skin closure.

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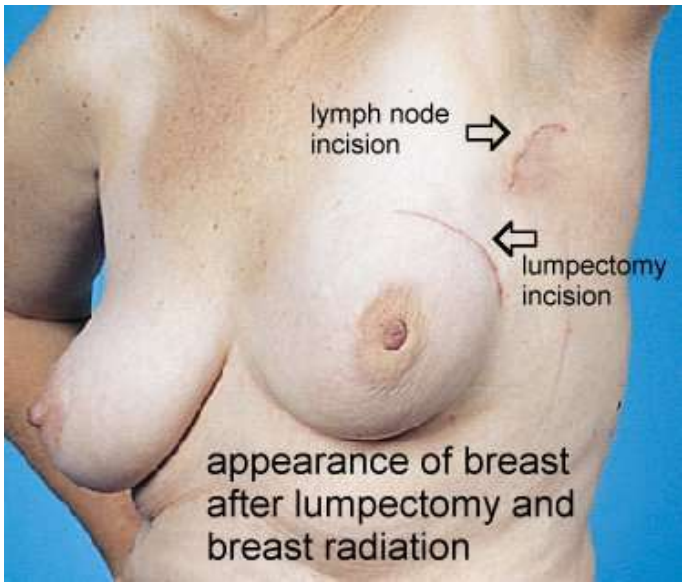
Surgical options

Lumpectomy Breast conservation surgery, lumpectomy followed by radiation, involves wide excision of the tumor with sentinel lymph node dissection (SLND) and/or axillary lymph node dissection (ALND). In some cases, breast conservation surgery may include partial or segmental mastectomy or quadrantectomy in order to obtain clean margins.



Prolonged radiation may result in change in texture and sensitivity of the breast. Impaired arm mobility may also occur, more often related to ALDN than SLND.

Breast conservation surgery is an option for those with tumors <4-5 cm with stage I or stage II breast cancer.

While there is a slightly increased chance of local recurrence of cancer with breast conservation surgery, this recurrence can usually be treated effectively with mastectomy.

Axillary lymph node dissection vs Sentinel lymph node biopsy

About two-thirds of women with early stage cancer show negative nodes on ALND, so SLND has become more commonly used as a less invasive alternative. ALND, which removes most of the axillary lymph nodes, may cause lymphedema, cellulitis (in 10-3%), decreased mobility of the arm, and changes in sensory perception. ALND is usually done under general anesthesia and SLND under local.

SLND has proven to have approximately the same degree of accuracy and recurrence rates as ALND. The sentinel lymph node (the first node) in the lymphatic basin is identified through injecting isotopes and/or dye. The surgeon uses a probe to locate the node and excise it. The node is usually examined with frozen section immediately. If the sentinel node is positive, then the surgeon continues with the more invasive ALND. SLND requires only a very small incision.

While SLND may result in similar symptoms as ALND, they are less common and usually less severe. For example, lymphedema occurs in only 0-7%. In both cases, a seroma (collection of serous fluid) may occur postoperatively.

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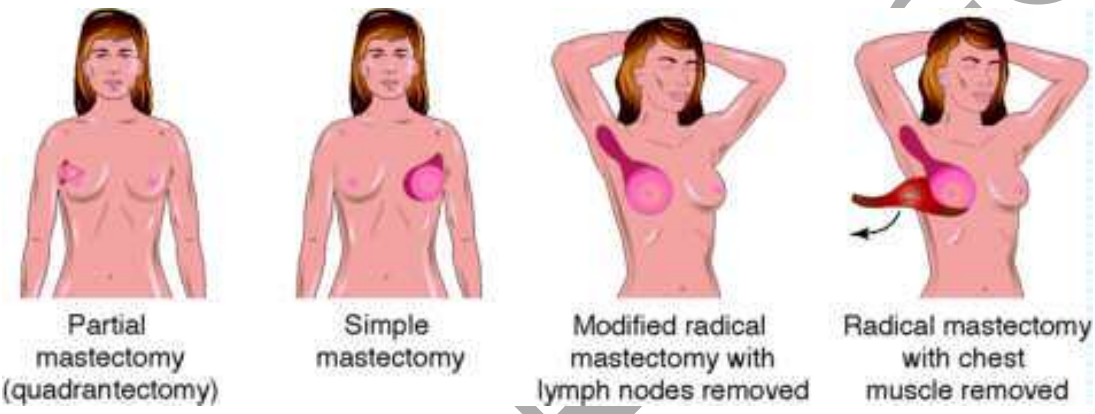
Mastectomy Multiple studies have demonstrated that lumpectomy with radiation is equivalent to mastectomy in rates of recurrence and survival. Despite this, many patients still choose mastectomy, for a variety of reasons:

- Concerns about radiation.
- Fear of recurrence.
- Better information about risk factors for recurrence.
- Availability of breast reconstruction.
- Skin-sparing and nipple-sparing mastectomy procedures.
- Surgeon preference.
- Lack of information about choices.



There has been a steady increase in recent years in the numbers of women who choose mastectomy as well as prophylactic mastectomy of the contralateral breast.

A number of different mastectomy procedures are available. The **radical mastectomy** with removal of the chest wall muscle, at one time the surgery of choice, is rarely done currently and is associated with significant pain and morbidity. The most common mastectomy procedures are the partial, simple (sometimes referred to as total mastectomy), and modified radical mastectomy with lymph node removal.

The **simple/total mastectomy** involves removal of the breast only but not the axillary lymph nodes.

The **modified radical mastectomy** involves removal of the entire breast

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tissue, including the nipple and areola. This procedure is usually done for those who don't qualify for breast conservation surgery or who opt for this procedure instead of breast conservation surgery.

Skin sparing mastectomy is now often used to allow for immediate breast reconstruction. The incision is usually smaller than with the traditional mastectomy, and the breast tissue is removed but the skin retained. The incision is made around the areola. Nipple reconstruction can be completed at a later time.

Subcutaneous mastectomy is sometimes used because it requires an incision under the breast and retains the nipple and areola so that breast reconstruction has little visible scarring. However, this procedure allows for less removal of breast tissue, so it's only considered appropriate for those requesting prophylactic mastectomy because of high risk (such as with BRCA1 or BRCA2 mutation). There still remains some risk of breast cancer, but the risk is far lower than without breast removal.

Nipple sparing mastectomy involves an incision around the nipple and areola. The nipple and areola are removed, scraped free of tissue, and then regrafted onto the breast after the tissue beneath the nipple is examined to ensure it's free of cancer. If cancer cells are present in the underlying tissue, then the nipple and areola are removed. While cosmetic results are fairly good, the shape of the nipple may change and flatten, and sensation is impaired.

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Skin sparing/Implants	Nipple sparing/Implants

Postoperative Care

Pain Pain varies depending on the extent of the surgery. Breast conservation surgery and SNLD usually involve minimal pain, but individuals vary widely in tolerance for pain, so pain should be assessed regularly and patients provided medications as needed. Pain may increase in the first few postoperative days as sensation returns to the operative area. Excruciating pain, especially if unrelieved by pain medication, may indicate development of an infection or hematoma.

Some patients experience a sensation of a "phantom" breast, feeling that the breast and nipple are present although this feeling is often not uncomfortable. Patients may, however, have other altered sensations because of damage to nerves during surgery: tenderness, soreness, numbness, tightness, pulling, and twinges.

Hematoma A collection of blood may occur in the surgical area, usually within the first 12 hours postoperatively. The patient may complain of a feeling of pain and tightness and the tissue may appear ecchymotic. Gross swelling or bloody discharge may indicate hemorrhage, which requires immediate attention of the surgeon and return to surgery.

If there appears to be only slow oozing of blood, a compression wrap may be applied to the surgical site for 12 hours. Small hematomas are absorbed by the body within 4-5 weeks. Warm showers or compresses may increase the rate of absorption.

Seroma A collection of fluid may occur in the surgical area or under the axilla, usually within 12 hours of surgery. Patients may complain of a feeling of heaviness or pain and fluid may be felt or heard sloshing on movement. If the drain is still in place, development of a seroma is an indication that the drainage tubing is blocked and may need to be unclogged. In some cases, fluid is removed by aspiration. Seromas may also develop after the drain is removed. Large seromas may result in infection if left in place, but small seromas usually absorb without intervention.

Lymphedema Lymphedema of the arm results from impaired lymphatic drainage after ALND and sometimes SLND. Collateral lymphatic circulation usually develops after removal of lymph nodes, so edema of the involved extremity is common in the early postoperative period before the

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collateral circulation develops; however, within a month, the circulation should return to normal and edema should recede.

Lymphedema is more likely to occur with more invasive procedures and may also result from damage caused by radiation. Risk also increases with chemotherapy, obesity, diabetes, and smoking.

In addition to swelling, some patients experience numbness, pain, and increased risk of infection. With persistent lymphedema, the symptoms don't recede and become chronic. Many patients benefit from referrals to physical therapist and/or occupational therapists. Treatment may include antibiotics for infection, a compression sleeve and/or glove, exercises, and manual lymph drainage. Symptoms are often increasingly difficult to manage over time.

If lymphedema becomes chronic, there is little chance it will improve, so preventive measures are critical. Preventive measures should begin immediately after surgery, and the patient should continue to follow the guidelines for prevention throughout life.

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Measures to prevent/control lymphedema
• Avoid the use of the affected extremity for blood pressure, blood draws, or injections. • Apply sunscreen when the extremity will be exposed to the sun for extended periods. • Apply insect repellent when necessary to prevent bug bites. • Shave underarms with electric razors. • Limit lifting to 5-10 pounds. • Avoid cutting cuticles during manicures. • Use cooking mitts when removing items from the oven or handling hot dishes to prevent burns.

Depression/ Impaired body image

Many patients are anxious about viewing their incision after surgery, especially those who have had a mastectomy, so patients should be encouraged to express their feelings and reassured that their feelings are normal.

It's important to remember when assessing patients that feeling of sadness and grief are normal and expected and do not necessarily indicate development of depression. Additionally, hormone suppressor drugs that initiate premature menopause may cause women to experience menopausal-like mood changes and hot flashes. All of these problems combined may result in chronic feelings of fatigue.

Some patients do become very depressed, especially if they have a poor self-image or have little partner support, and these patients may benefit from antidepressants and counseling. Indications of clinical depression include:

- Inability to cope.
- Feelings of hopelessness and helplessness.
- Poor concentration.
- Impaired memory.
- Panic attacks.
- Lack of feelings of pleasure.
- Lack of interest in food.
- Lack of interest in sex.
- Insomnia or hypersomnia.

If patients have not had implants inserted during surgery, they should be provided temporary breast forms before leaving the hospital to relieve self-consciousness about their appearance. Providing both the patient and partner with as much information as possible both before and after surgery may help to alleviate some anxiety, but support may need to be ongoing. Breast cancer survivor groups may provide women with necessary support. Other resources include message boards and online support groups.

Some patients are especially concerned if they require chemotherapy or radiation because they are fearful of the side effects, so they must be provided information about possible side effects and methods of dealing with side effects.

Impaired sexual function occurs frequently. One study of 1700 breast cancer survivors found 70% experienced sexual dysfunction 2 years after diagnosis and initial treatment. Some expressed concerns over body image and other of symptoms related to forced menopause. Patients may need counselling to assist with sexual functioning.

Infection Infection is not common, but may occur, especially in those who are older adults or have diabetes or immune

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disorders. Indications include fever (>100.4°F/38°C), malaise, erythema and warmth about incision, tenderness, foul-smelling drainage. Treatment includes taking wound culture if discharge is evident and oral or IV antibiotics (depending on the severity of the infection).

Conclusion

With early detection, cancer survival rates are very good. The National Cancer Data Base provides the following information:

Stage	5-year survival rate
0	93%
I	88%
IIA	81%
IIB	74%
IIIA	67%
IIIB	41%*
IIIC	49%*
IV	15%

Patients with stage III or stage IV cancer face increased risk of recurrence and metastasis. Approximately 40% of those diagnosed with breast cancer experience recurrence, and approximately 40,000 women die with breast cancer each year. Recurrence is most common within the first 3-5 years although delayed recurrence does happen with some patients. Recurrence may occur locally or with distant metastasis. With recurrence, many factors must be considered when determining the optimal treatment.

With local recurrence after lumpectomy, a mastectomy is usually done. With local recurrence after mastectomy, the new tumor is removed, usually followed by radiotherapy. Different chemotherapy protocols may be used with or without hormone suppression and/or targeted therapy.

A patient may or may not be able to have further radiation to the breast, depending on the amount of radiation previously delivered to the site, as there is a tissue maximum although the patient may receive palliative radiation to other sites even if the breast area has received the maximum dosage.

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