NEWER TREATMENT MODALITIES IN MANAGEMENT OF BREAST CANCER

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ABSTRACT

Breast cancer is a malignant (cancer) tumor that starts in the cells of the breast. Breast cancer is a leading cause of morbidity and mortality in women worldwide. Breast screening in normal and/or asymptomatic women is essential to reduce the burden of breast malignancies. Breast cancer is a leading cause of morbidity and mortality in women worldwide. Breast screening in normal and/or asymptomatic women is essential to reduce the burden of breast malignancies. A majority of Indian breast cancer patients self-detect any clinically relevant breast abnormality such as a palpable lump, or at a stage when there are secondary manifestations such as local skin or chest wall changes and/or distant metastases. Abnormal BRCA1 and BRCA2 genes may account for up to 10\% of all breast cancers. Main challenges for breast imaging in India include a large number of women presenting with advanced breast cancers, inadequate breast imaging facilities and its variable quality. This review emphasizes on current trends, imaging and treatment options for Breast Cancer.

KEYWORDS: Abnormal BRCA1, BRCA2, asymptomatic.

INTRODUCTION

Breast cancer is the most commonly occurring cancer among women, causing more deaths in the world than any other cancer except lung cancer. It accounts for nearly 21\% of all cancers.
among women worldwide. The highest incidence occurs in the developed countries. In America, 1 out of every 8 women has invasive breast cancer, which is responsible for almost 3% of all deaths in American women. While in India, breast cancer accounts for 22.2% of new cancer cases and 7% of cancer deaths annually among women. Between 2002 and 2020, breast cancer incidence and mortality are expected to rise 50%, with the greatest rise occurring in developing countries. In USA breast cancer becomes the most common cancer. The incidence rates of breast cancer are high in North America, Northern and Western Europe, intermediate in South America and Southern Europe and low in Africa and Asia. The cause of breast cancer is complex and not fully understood.

Breast cancer is a malignant tumor that starts in the cells of the breast. A malignant tumor is a group of cancer cells that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. The disease occurs almost entirely in women, but men can get it, too. To understand breast cancer, one should have some basic knowledge about the normal structure of the breasts, shown in the diagram below (Figure 1).

![Figure 1: Anatomy of breast](image)

The breast is composed mainly of fatty tissue, which contains a network of lobes made up of tiny, tube-like structures called lobules that contain milk glands. Tiny ducts connect the glands, lobules, and lobes, and carry the milk from the lobes to the nipple. Blood and lymph vessels run throughout the breast. About 90% of all breast cancers originate in the ducts or lobes of the breast.

Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in other tissues.
Types of Breast Cancer in women

Breast Cancer type can be broadly classified as non-invasive (in situ) and invasive (infiltrating). Also they can be separated into several types based on the way the cancer cells look under the microscope. Various types are as follows-

1. Ductal Carcinoma In-situ
2. Invasive (or infiltrating) ductal carcinoma
3. Invasive (or infiltrating) lobular carcinoma

Less common types of breast cancer are inflammatory breast cancer, paget disease of the nipple, phyllodes tumor, and angiosarcoma.\[3\]

Sub-types of invasive carcinoma are

- Adenoid cystic (or adenocystic) carcinoma.
- Low-grade adenosquamous carcinoma (this is a type of metaplastic carcinoma).
- Medullary carcinoma.
- Mucinous (or colloid) carcinoma.
- Papillary carcinoma.
- Tubular carcinoma.
- Metaplastic carcinoma (most types, including spindle cell and squamous).
- Micropapillary carcinoma.
- Mixed carcinoma (has features of both invasive ductal and lobular).

Breast cancer may also occur in men. Men at any age may develop breast cancer, but it is usually detected (found) in men between 60 and 70 years of age. Male breast cancer makes up less than 1% of all cases of breast cancer.\[4\]
Risk Factors

The risk factors influencing breast cancer risk are broadly classified into modifiable and non-modifiable factors. The non-modifiable risk factors are age, gender, number of first degree relatives suffering from breast cancer, menstrual history, age at menarche and age at menopause. While the modifiable risk factors are BMI, age at first child birth, number of children, duration of breast feeding, alcohol, diet and number of unsuccessful pregnancies (abortions).[5]
Screening
The women with higher risk of developing breast cancer may be offered screening and genetic testing for the disease. Screening is especially recommended for women with risk factors, a significant one being family history.\(^6\) Having a 1st-degree relative (mother, sister, and daughter) with breast cancer doubles or triples the risk of developing the cancer. About 5% of women with breast cancer carry a mutation in one of the 2 known breast cancer genes, BRCA1 or BRCA2. If relatives of such a woman also carry the gene, they have a 50 to 85% lifetime risk of developing breast cancer. Heightened awareness of breast cancer risk in the past decades has led to an increase in the number of women undergoing mammography for screening, leading to detection of cancers in earlier stages and an improvement in survival rates. Approximately 20% of the cancers detected in a given year will be missed at the screening, but will become clinically evident in the period before the next screen (interval cancers).\(^7\)

Pathology and pathophysiology
The various abnormalities of the breast include nipple discharge, inflammations, ANDI, benign disorders, phyllodes / sarcomas and carcinoma Most breast cancers are epithelial tumors that develop from cells lining ducts or lobules; less common are nonepithelial cancers of the supporting stroma (e.g., angiosarcoma, primary stromal sarcomas, phyllodes tumor). Cancers are divided into carcinoma in situ and invasive cancer.\(^8\) Paget's disease of the nipple is a form of ductal carcinoma in situ that extends into the overlying skin of the nipple and areola, manifesting with an inflammatory skin lesion and may become invasive. The
pathological variations of breast cancer influence the prognosis. In situ cancers (DCIS/LCIS) are slow growing, indolent tumors. Autopsy studies have indicated that the incidence of DCIS in asymptomatic women ranges from .02% to 18.2% indicating that some DCIS do not become evident during a women’s lifetime. Invasive carcinoma is primarily adenocarcinoma. About 80% is the infiltrating ductal type; most of the remainder is infiltrating lobular. The pathological variants with a favorable prognosis are tubular, cribriform, mucinous and adenoid cystic variants, while intermediate prognosis is seen with medullary, secretory and invasive lobular cancers. The most unfavorable pathology is high grade metaplastic, micropalliary, signet ring cell morphology, inflammatory cancer. Breast cancer invades locally and spreads initially through the regional lymph nodes, bloodstream, or both. Metastatic breast cancer may affect almost any organ in the body—most commonly, lungs, liver, bone, brain, and skin.

**Signs and symptoms**

Most breast cancers present as a lump felt by the patient or during routine physical examination or mammography. Less commonly, the presenting symptom is thickening in the breast. Paget's disease of the nipple presents with skin changes, including erythema, crusting, scaling, and discharge. A few patients with breast cancer present with signs of metastatic disease (eg, pathologic fracture, pulmonary dysfunction).

During a physical examination a lump is felt distinctly different from the surrounding breast tissue. More advanced breast cancers are characterized by fixation of the lump to the chest wall or to overlying skin, by satellite nodules or ulcers in the skin.

![Figure 6: Signs and symptoms of breast cancer](image-url)
Matted or fixed axillary lymph nodes suggest tumor spread. Inflammatory breast cancer is characterized by diffuse inflammation and enlargement of the breast, often without a lump, and has a particularly aggressive course.

**Staging of Breast cancer**

The staging systems currently in use for breast cancer are based on the clinical size and extent of invasion of the tumor. Stages of breast cancer are mainly classified into five categories by the Union International Centre Cancer (UICC), which are the following.\(^{13}\)

![Figure 7: Stages of breast cancer](image)

**Stage 0:** It is also called as carcinoma in situ (lobular carcinoma in situ and ductal carcinoma in situ). The cancer is still in the place where it first developed. This is the earliest stage of breast cancer.

**Stage 1:** In stage I, size of tumor is smaller than 2 cm. It does not appear to have spread beyond the breast.

**Stage II:** Under this stage, size of tumor is either less than 2 cm across and has spread to the lymph nodes under the arm; or the tumor is between 2 and 5 cm (with or without spread to the lymph nodes under the arm); or the tumor is greater than 5 cm and hasn't spread outside the breast.

**Stage III:** In this stage, tumor is greater than 5 cm across and/or has spread to axillary lymph nodes that are attached to one another or nearby tissue. Breast cancer tumors of any size, which have spread to the skin, the chest wall, or lymph nodes (which those under the breast or inside the chest) are also included in this stage.
Stage IV: Metastatic breast cancer where the cancer has spread outside the breast to other organs in the body.

Diagnosis of Breast cancer
If there are any signs or symptoms that might mean breast cancer, be sure to see oncologist as soon as possible. Breasts will be thoroughly examined for any lumps or suspicious areas and to feel their texture, size, and relationship to the skin and chest muscles. Any changes in the nipples or the skin of your breasts will be noted. The lymph nodes in your armpit and above your collarbones may be palpated (felt), because enlargement or firmness of these lymph nodes might indicate spread of breast cancer. Your doctor will also do a complete physical exam to judge your general health and whether there is any evidence of cancer that may have spread.[14]

If breast symptoms and/or the results of your physical exam suggest breast cancer might be present, more tests will probably be done. These might include imaging tests, looking at samples of nipple discharge, or doing biopsies of suspicious areas.[15]

Imaging tests used to evaluate breast disease
Imaging tests use x-rays, magnetic fields, sound waves, or radioactive substances to create pictures of the inside of your body. Imaging tests may be done for a number of reasons, including to help find out whether a suspicious area might be cancerous, to learn how far cancer may have spread, and to help determine if treatment is working.[16]

Diagnostic mammograms
A mammogram is an x-ray of the breast. Screening mammograms are used to look for breast disease in women who have no signs or symptoms of a breast problem. Screening mammograms usually take 2 views (x-ray pictures taken from different angles) of each breast. Diagnostic mammograms are used to diagnose breast disease in women who have breast symptoms (like a lump or nipple discharge) or an abnormal result on a screening mammogram. A diagnostic mammogram includes more images of the area of concern. In some cases, special images known as cone or spot views with magnification are used to make a small area of abnormal breast tissue easier to evaluate.[18]
A diagnostic mammogram shows

- That the abnormality is not worrisome at all. In these cases the woman can usually return to having routine yearly mammograms.
- That a lesion (area of abnormal tissue) has a high likelihood of being benign (not cancer). In these cases, it is common to ask the woman to come back sooner than usual for her next mammogram, usually in 4 to 6 months.
- That the lesion is more suspicious, and a biopsy is needed to tell if it is cancer.

Even if the mammograms show no tumor, if you or your doctor can feel a lump, a biopsy is usually needed to make sure it isn't cancer. One exception would be if an ultrasound exam finds that the lump is a simple cyst (a fluid-filled sac), which is very unlikely to be cancerous. If cancer is found, a diagnostic mammogram is often done to get more thorough views of the breasts. This is to check for any other abnormal areas that could be cancer as well.\textsuperscript{[19]}

**Figure 8: Mammography**

**Breast ultrasound**

Ultrasound, also known as sonography, uses sound waves to outline a part of the body. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is often first lubricated with ultrasound gel). It emits sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image that is displayed on a computer screen. This test is painless and does not expose you to radiation.\textsuperscript{[20]}

Ultrasound has become a valuable tool to use along with mammography because it is widely available and less expensive than other options, such as MRI. Usually, breast ultrasound is used to target a specific area of concern found on the mammogram. Ultrasound helps
distinguish between cysts (fluid-filled sacs) and solid masses and sometimes can help tell the
difference between benign and cancerous tumors. In someone with a breast tumor, it can also
be used to look for enlarged lymph nodes under the arm.\textsuperscript{[21]}

The use of ultrasound instead of mammograms for breast cancer screening is not
recommended. However, clinical trials are now looking at the benefits and risks of adding
breast ultrasound to screening mammograms in women with dense breasts and a higher risk
of breast cancer.

\textbf{Magnetic resonance imaging (MRI) of the breast}

MRI can be used along with mammograms for screening women who have a high risk of
developing breast cancer, or it can be used to better examine suspicious areas found by a
mammogram. MRI is also sometimes used for women who have been diagnosed with breast
cancer to better determine the actual size of the cancer and to look for any other cancers in
the breast. It is not yet clear how helpful this is in planning surgery in someone known to
have breast cancer. In someone known to have breast cancer, it is sometimes used to look at
the opposite breast; to be sure that it does not contain any tumors. If an abnormal area in the
breast is found, it can often be biopsied using an MRI for guidance. This is discussed in more
detail in the "Biopsy" section.\textsuperscript{[22]}

\textbf{Ductogram}

This test, also called a Galactogram, sometimes helps determine the cause of nipple
discharge. In this test a very thin plastic tube is placed into the opening of the duct in the
nipple that the discharge is coming from. A small amount of contrast medium is injected,
which outlines the shape of the duct on an x-ray image and shows if there is a mass inside the
duct.\textsuperscript{[23]}

\textbf{Nipple discharge exam}

If there is any nipple discharge, some of the fluid may be collected and looked at under a
microscope to see if any cancer cells are in it. Most nipple discharges or secretions are not
cancer. In general, if the secretion appears milky or clear green, cancer is very unlikely. If the
discharge is red or red-brown, suggesting that it contains blood, it might possibly be caused
by cancer, although an injury, infection, or benign tumors are more likely causes.\textsuperscript{[24]}
Even when no cancer cells are found in a nipple discharge, doctors cannot be sure breast cancer is not present. If you have a suspicious mass, it will be necessary to biopsy the mass, even if the nipple discharge does not contain cancer cells.

**Ductal lavage and nipple aspiration**

Ductal lavage is an experimental test developed for women who have no symptoms of breast cancer but are at very high risk for the disease. It is not a test to screen for or diagnose breast cancer, but it may help give a more accurate picture of a woman's risk of developing it.\[25\]

Ductal lavage can be done in a doctor's office or an outpatient facility. An anesthetic cream is applied to numb the nipple area. Gentle suction is then used to help draw tiny amounts of fluid from the milk ducts up to the nipple surface, which helps locate the ducts' natural openings. A tiny tube (called a catheter) is then inserted into a duct opening. Saline (salt water) is slowly infused into the catheter to gently rinse the duct and collect cells. The ductal fluid is drawn through the catheter and sent to a lab, where the cells are looked at under a microscope. Ductal lavage is not done if women aren’t at high risk for breast cancer. It is not clear if it will ever be useful. The test has not been shown to detect cancer early. It is more likely to be helpful as a test of cancer risk rather than as a screening test for cancer. More studies are needed to better define the usefulness of this test.\[26\]

Nipple aspiration also looks for abnormal cells developing in the ducts, but is much simpler, because nothing is inserted into the breast. The device for nipple aspiration uses small cups that are placed on the woman's breasts. The device warms the breasts, gently compresses them, and applies light suction to bring nipple fluid to the surface of the breast. The nipple fluid is then collected and sent to a lab for analysis. As with ductal lavage, the procedure may be useful as a test of cancer risk but is not an appropriate screening test for cancer. The test has not been shown to detect cancer early.\[27\]

**Biopsy**

A biopsy is done when mammograms, other imaging tests, or the physical exam finds a breast change (or abnormality) that is possibly cancer. A biopsy is the only way to tell if cancer is really present. During a biopsy, a sample of the suspicious area is removed to be looked at under a microscope, by a specialized doctor with many years of training called a pathologist. The pathologist sends your doctor a report that gives a diagnosis for each sample taken.\[28\]
There are several types of biopsies, such as fine needle aspiration biopsy, core (large needle) biopsy, and surgical biopsy. Each has its pros and cons. The choice of which to use depends on your specific situation. Some of the factors your doctor will consider include how suspicious the lesion appears, how large it is, where in the breast it is located, how many lesions are present, other medical problems you might have, and your personal preferences.\(^\text{[29]}\)

Often, after the tissue sample is removed, the doctor will place a tiny metal clip or marker inside the breast at the biopsy site. The clip cannot be felt and should not cause any problems, but it is helpful in finding the area again on future mammograms and for surgery. Some patients who have cancer are given chemotherapy or other treatments before surgery that can shrink the tumor so much that it can’t be felt or seen on mammogram. The clip can be used to direct the surgeon to the area where the tumor was so the correct area of the breast can be removed.\(^\text{[30]}\)

**Fine needle aspiration biopsy**

In a fine needle aspiration (FNA) biopsy, the doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from a suspicious area, which is then looked at under a microscope. The needle used for an FNA biopsy is thinner than the one used for blood tests.\(^\text{[31]}\)

If the area to be biopsied can be felt, the needle can be guided into the area of the breast change while the doctor is feeling (palpating) it.

If the lump can't be felt easily, the doctor might use ultrasound to watch the needle on a screen as it moves toward and into the mass. A local anesthetic (numbing medicine) may or may not be used. Because such a thin needle is used for the biopsy, the process of getting the anesthetic may actually be more uncomfortable than the biopsy itself. Once the needle is in place, fluid is drawn out. If the fluid is clear, the lump is probably a benign cyst. Bloody or cloudy fluid can mean either a benign cyst or, very rarely, a cancer. If the lump is solid, small tissue fragments are drawn out. A pathologist will look at the biopsy tissue or fluid under a microscope to determine if it is cancerous. An FNA biopsy is the easiest type of biopsy to have, but it has some disadvantages. It can sometimes miss a cancer if the needle is not placed among the cancer cells. And even if cancer cells are found, it is usually not possible to determine if the cancer is invasive. In some cases there may not be enough cells to perform
some of the other lab tests that are routinely done on breast cancer specimens. If the FNA biopsy does not provide a clear diagnosis, or your doctor is still suspicious, a second biopsy or a different type of biopsy should be done.\textsuperscript{[31]}

**Core needle biopsy**
A core biopsy uses a larger needle to sample breast changes felt by the doctor or pinpointed by ultrasound or mammogram.

When mammograms taken from different angles are used to pinpoint the biopsy site, this is known as a stereotactic core needle biopsy. In some centers, the biopsy can be guided by an MRI scan. The needle used in core biopsies is larger than the one used in FNA.\textsuperscript{[32]} It removes a small cylinder (core) of tissue (about 1/16- to 1/8-inch in diameter and ½-inch long) from a breast abnormality. Several cores are often removed. The biopsy is done using local anesthesia (you are awake but the area is numbed) in an outpatient setting. Because it removes larger pieces of tissue, a core needle biopsy is more likely than an FNA to provide a clear diagnosis, although it might still miss some cancers.\textsuperscript{[33]}

**Vacuum-assisted core biopsies**
Another way to do a core biopsy is known as vacuum-assisted. For this procedure, the skin is numbed and a small incision (about ¼ inch) is made. A hollow probe is inserted through the incision into the abnormal area of breast tissue. The probe is guided into place using mammography, ultrasound, or MRI.\textsuperscript{[34]} A cylinder of tissue is then suctioned in through a hole in the side of the probe, and a rotating knife within the probe cuts the tissue sample from the rest of the breast. Several samples can be taken from the same incision. Vacuum-assisted biopsies are done as an outpatient procedure. No stitches are needed, and there is minimal scarring. This method usually removes more tissue than a regular core biopsy.

**Surgical (open) biopsy**
Usually, breast cancer can be diagnosed using needle biopsy. Rarely, surgery is needed to remove all or part of the lump for microscopic examination. This is referred to as a surgical biopsy or an open biopsy. Most often, the surgeon removes the entire mass or abnormal area as well as a surrounding margin of normal-appearing breast tissue. This is called an excisional biopsy. If the mass is too large to be removed easily, only part of it may be removed.\textsuperscript{[34]} This is called an incisional biopsy. In rare cases, a surgical biopsy can be done in the doctor's office, but it is most often done in the hospital's outpatient department under local
anesthesia (you are awake, but your breast is numbed), often with intravenous sedation (medicine given to make you drowsy). This type of biopsy can also be done under general anesthesia (you are asleep). If the breast change cannot be felt, a mammogram may be used to place a wire into the correct area to guide the surgeon. This technique is called wire localization or stereotactic wire localization. After the area is numbed with local anesthetic, a thin hollow needle is placed in the breast, and x-ray views are used to guide the needle to the suspicious area. Once the tip of the needle is in the right spot, a thin wire is inserted through the center of the needle. A small hook at the end of the wire keeps it in place. The hollow needle is then removed. The surgeon can then use the wire as a guide to the abnormal area to be removed. The surgical specimen is sent to the lab to be looked at under a microscope. Core needle biopsy is usually enough to make a diagnosis, but sometimes an open biopsy may be needed depending on where the lesion is, or if a core biopsy is not conclusive.

**Lymph node biopsy**

If the lymph nodes under the arm are enlarged (either by feel or on an imaging test like mammography or ultrasound); they may be checked for cancer spread. Most often, a needle biopsy is done at the time of the needle biopsy of the breast tumor. Even if no lymph nodes are enlarged, the lymph nodes under the arm are usually checked for cancer spread when the breast tumor is removed at surgery. This is done with a sentinel lymph node biopsy and/or an axillary lymph node dissection.

**Tests to detect breast cancer**

**Estrogen and progesterone receptor test**

A test to measure the amount of estrogen and progesterone (hormones) receptors in cancer tissue. If there are more estrogen and progesterone receptors than normal, the cancer may grow more quickly. The test results show whether treatment to block estrogen and progesterone may stop the cancer from growing.

**Human epidermal growth factor type 2 receptor (HER2/neu) test**

A laboratory test to measure how many HER2/neu genes there are and how much HER2/neu protein is made in a sample of tissue. If there are more HER2/neu genes or higher levels of HER2/neu protein than normal, the cancer may grow more quickly and is more likely to spread to other parts of the body. The cancer may be treated with drugs that target the HER2/neu protein, such as trastuzumab and lapatinib.
**Multigene tests**
Tests in which samples of tissue are studied to look at the activity of many genes at the same time. These tests may help predict whether cancer will spread to other parts of the body or recur (come back).

**Oncotype DX**
This test helps predict whether stage I or stage II breast cancer that is estrogen receptor positive and node-negative will spread to other parts of the body. If the risk of the cancer spreading is high, chemotherapy may be given to lower the risk.

**MammaPrint**
This test helps predict whether stage I or stage II breast cancer that is node-negative will spread to other parts of the body. If the risk of the cancer spreading is high, chemotherapy may be given to lower the risk.\(^{[39]}\)

**Test to find out whether the cancer has been spread to other parts of Body**

**Sentinel lymph node biopsy**
The removal of the sentinel lymph node during surgery. The sentinel lymph node is the first lymph node to receive lymphatic drainage from a tumor. It is the first lymph node the cancer is likely to spread to from the tumor. A radioactive substance and/or blue dye is injected near the tumor. The substance or dye flows through the lymph ducts to the lymph nodes. The first lymph node to receive the substance or dye is removed. A pathologist views the tissue under a microscope to look for cancer cells. If cancer cells are not found, it may not be necessary to remove more lymph nodes.\(^{[40]}\)

**Chest x-ray**
An x-ray of the organs and bones inside the chest. An x-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body.

**CT scan (CAT scan)**
A procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.\(^{[41]}\)
Bone scan
A procedure to check if there are rapidly dividing cells, such as cancer cells, in the bone. A very small amount of radioactive material is injected into a vein and travels through the bloodstream. The radioactive material collects in the bones and is detected by a scanner.

PET scan (positron emission tomography scan)
A procedure to find malignant tumor cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

Management of breast cancer
Breast cancer can be treated using a multimodality approach of surgery, chemotherapy, radiotherapy and targeted therapy. The treatment options vary as per the stage of the tumor.

Chemotherapy
Chemotherapy is systemic drug treatment intended to stop cancer cells from dividing and growing. Chemotherapy is often associated with unpleasant side effects since it targets all rapidly growing cells, in addition to cancer cells. [42]

Figure 11: Classification of chemotherapeutic drugs
Table 1: Examples of Chemotherapeutic drugs in market.

<table>
<thead>
<tr>
<th>Types of Chemotherapy drugs</th>
<th>Drugs approved by USFDA</th>
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<tbody>
<tr>
<td>Alkylating Agents</td>
<td>Cytoxan® / Cyclophosphamide Thiotepa</td>
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<tr>
<td>Anthracyclines</td>
<td>Adriamycin® / Doxorubicin Doxil® / Liposomal Doxorubicin Ellence® / Epirubicin Novantrone® / Mitoxantrone</td>
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<tr>
<td>Platinum Drugs</td>
<td>Paraplatin® / Carboplatin Platinol® / Cisplatin</td>
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<tr>
<td>Taxanes</td>
<td>Abraxane® / Paclitaxel Protein-bound Taxol® / Paclitaxel Taxotere® / Docetaxel</td>
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<tr>
<td>Vinca Agents</td>
<td>Navelbine® / Vinorelbine</td>
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<tr>
<td>Other Chemotherapy drugs</td>
<td>Adrucil® / Fluorouracil (5-FU) Camptosor® / Irinotecan Gemzar® / Gemcitabine Halaven® / Eribulin Ixempra® / Ixabepilone Methotrexate Temodar® / Temozolomide Topotecan Vincristine Vinblastine Xeloda® / Capecitabine</td>
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Common Chemotherapy Regimens for Metastatic Breast Cancer
- Taxol® + Xeloda®.
- Taxotere® + Xeloda®.
- Taxotere® + Carboplatin.
- Taxol® + Carboplatin.
- Taxol® + Gemzar®.
- Abraxane® + Xeloda®.
- Abraxane® + Carboplatin.
- Irinotecan + Temozolomide.
- Gemzar® + Carboplatin.
- Ixempra® + Xeloda®.

Hormone Therapy
Hormonal therapies are intended to prevent hormone-receptor positive cells from being exposed to the hormones that cause them to grow; they are used in both prevention and
treatment. There are three main types of hormone therapies: anti-estrogen drugs, aromatase inhibitors, and ovarian suppressors.[43]

**Anti-Estrogen Drugs**
Anti-estrogen drugs block the effects of estrogen in the breast by binding to estrogen receptors on tumor cells. By attaching themselves to receptors, anti-estrogens prevent the cell from responding to estrogen's growth-promoting activities. Raloxifene is an anti-estrogen drug approved for prevention of breast cancer by the FDA.

Aromatase Inhibitors: These drugs block aromatase, a molecule required to produce estrogen. Aromatase inhibitors are only effective in postmenopausal women whose ovaries are no longer producing estrogen.

**Ovarian Suppression**
Suppressing the ability of the ovaries to produce estrogen is a viable treatment for estrogen-sensitive breast tumors in premenopausal women.

**Table 2: Examples of hormone therapy drugs in market**

<table>
<thead>
<tr>
<th>Types of Hormonal Drugs</th>
<th>Drugs approved by USFDA</th>
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<tbody>
<tr>
<td><strong>Anti-Estrogen Drugs</strong></td>
<td>Evista® / Raloxifene</td>
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<td>Fareston® / Toremifine</td>
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<td></td>
<td>Faslodex® / Fulvestrant</td>
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<td></td>
<td>Nolvadex® / Tamoxifen</td>
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<tr>
<td><strong>Aromatase Inhibitors</strong></td>
<td>Arimidex / Anastrozole</td>
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<td></td>
<td>Aromasin / Exemestane</td>
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<td>Femara / Letrozole</td>
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<td><strong>Ovarian Suppression</strong></td>
<td>Lupron® / Leuprolide</td>
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<tr>
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<td>Plenaxis® / Abarelix</td>
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<td>Suprefact® / Buserlin</td>
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<td>Zoladex® / Goserelin</td>
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<tr>
<td><strong>Other Endocrine/Hormone Therapy</strong></td>
<td>Megace® / Megestrol Acetate</td>
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**Bisphosphonate Therapy**
Bisphosphonate therapy, commonly used for osteoporosis, is also used to treat breast cancer that has spread to the bones. Bisphosphonate therapy is also prescribed for patients who are taking aromatase inhibitors for early stage breast cancer, since in some patients, aromatase inhibitors weaken bone.

- Actonel® / Risedronate.
- Aredia® / Pamidronate.
• Boniva® / Ibandronate.
• Fosamex® / Alendronate.
• Xgeva® / Denosumab.
• Zometa® / Zoledronate.

**Targeted Biological Therapy:** Targeted/biological therapies (or immune targeted therapies) focus on blocking the actions of certain normal body proteins that allow cancer cells to grow and divide. These treatments target cancer cells, lessening toxicity and reducing side effects.\(^{[44]}\)

• **Afinitor® / Everolimus:** Everolimus is a targeted therapy that acts by inhibiting an enzyme involved in cancer cell growth. Everolimus specifically targets a protein kinase enzyme called mammalian target of rapamycin (mTOR).

• **Avastin® / Bevacizumab:** is an anti-angiogenesis targeted therapy. Anti-angiogenesis therapy works by cutting off the blood supply of tumors, which limits tumor growth

• **Herceptin® / Trastuzumab:** Both a targeted and biological therapy, Herceptin® is a monoclonal antibody that specifically attaches to the HER2/neu receptor. Located on the cell surface, the HER2/neu receptor normally binds to a growth-promoting agent. By binding to this receptor, Herceptin® prevents the normal growth factor from signaling the tumor cell to divide.

• **Kadcyla® / T-DM1 (Ado-trastuzumab emtansine):** Kadcyla combines Herceptin and a chemotherapy drug (DM1) that interferes with cancer cell growth. Kadcyla delivers Herceptin and DM1 directly to HER2-positive cells, and limits exposure of the rest of the body to the chemotherapy.

• **Lapatinib® / Tykerb** targets tumor cells that express the HER2/neu protein. In contrast to Herceptin®, Lapatinib blocks the HER2/neu protein inside the cell rather than at the cell surface.

• **Perjeta® / Pertuzumab:** Perjeta works by targeting a different part of the HER2 protein than Herceptin, resulting in further reduction in growth of HER2-positive breast cancer cells.
Surgery
The goal of breast cancer surgery is to remove the entire tumor from the breast. Some of the lymph nodes from the underarm area (axillary nodes) may also be removed to see if cancer cells are present. There are two basic types of surgery to remove breast cancer:
• Lumpectomy (also called breast-conserving surgery or wide excision)
• Mastectomy

With lumpectomy, the tumor and a small rim of normal tissue surrounding the tumor are removed, but the rest of the breast remains intact. With mastectomy, the entire breast is removed. Almost all women who have lumpectomy will have radiation therapy to the breast after surgery. Some women who have mastectomy may also have radiation therapy.

Figure 12: Types of surgery in breast cancer

Lumpectomy
Lumpectomy (also known as breast conserving surgery or wide excision) is a surgery to remove cancer from the breast. Unlike a mastectomy, a lumpectomy removes only the tumor and a small rim (area) of the normal tissue around it. So, the breast looks as close as possible to how it did before surgery. Most often, the general shape of the breast and the nipple area are kept. Radiation therapy is given after lumpectomy to get rid of any cancer cells that may remain. This lowers the chances of the cancer returning to the breast to about five to 10 percent. Overall survival with lumpectomy plus radiation therapy is the same as with mastectomy. After lumpectomy you may have chemotherapy, hormone therapy and/or targeted therapy. Lumpectomy (also called breast conserving surgery or wide excision) is
often done under general anesthesia, which means you are unconscious (asleep) during the surgery. In some cases, regional anesthesia may be used.[46]

The surgeon makes an incision (cut) in the breast and removes the tumor, along with a small rim (area) of normal tissue surrounding the tumor. He/she then closes the incision with stitches, trying to keep the breast looking as much like it did before surgery. The surgeon may also make an incision in the underarm area and remove some lymph nodes. In some cases, more than one surgery is needed to get clean margins. Clean (also called uninvolved or negative) margins mean there is only normal tissue (and no cancer cells) at the edges of the tissue removed from the breast. Learn more about assessing margins. The tissue removed during surgery is sent to a pathologist for detailed testing. Learn about the results of the tests and other information found in your pathology report.

**Mastectomy**

Mastectomy is the surgical removal of the entire breast. Some women have the option of mastectomy or lumpectomy (also called breast conserving surgery) plus radiation. Other women can only have mastectomy. Mastectomy is an option for all women with breast cancer, including those who have:

- Ductal carcinoma in situ (DCIS).
- Early breast cancer.
- Locally advanced breast cancer.
- Inflammatory breast cancer.
- Paget disease of the breast (Paget disease of the nipple).

Mastectomy is also used to treat breast cancer that has come back after a lumpectomy. There are two general types of mastectomy: total (simple) and modified radical. Your diagnosis guides which type of mastectomy you will have. A mastectomy is performed under general anesthesia, which means you are unconscious (asleep) during the surgery. The surgeon removes all of the breast tissue (in most cases, but not all, the nipple and areola are also removed). The lining of the chest muscles may also be removed.[47]
Radiation therapy

Two main drawbacks of radiation therapy are the frequency and length of the treatment. Treatment is usually given once a day, five days a week, for three to seven weeks. Techniques that shorten the course of treatment continue to be studied in clinical trials. The results of these trials will decide whether these therapies become part of standard care. After talking with your health care provider, we encourage you to consider joining a clinical trial of radiation therapy for breast cancer. Accelerated partial breast irradiation: Accelerated partial breast irradiation delivers radiation only to the area around the tumor bed (the tissue in and around the space where the tumor was removed during lumpectomy). This reduces the number of treatment sessions (accelerated therapy). Not everyone can have this type of radiation therapy. Accelerated partial breast irradiation can be done by brachytherapy, three-dimensional conformal external beam or by intraoperative radiation therapy. These techniques are still under study.\[^{48}\]

Brachytherapy

Brachytherapy uses targeted radiation therapy placed inside the tumor bed. Implanted radiation "seeds" (interstitial radiation therapy) or a single small balloon device (intracavitary radiation therapy) can be used to deliver the radiation.

Some early findings suggest accelerated partial breast irradiation with brachytherapy may be as effective as standard radiation therapy in reducing rates of breast cancer recurrence.\[^{19-22}\] However, follow-up time on these studies is short and the long-term effects of brachytherapy are not yet known. It is also not clear which women are the best candidates for brachytherapy.
and whether the cosmetic look of the breast is as good with brachytherapy as with standard radiation therapy.\textsuperscript{[14,22]} Although brachytherapy is available at some medical centers and may be appropriate in select cases, its long-term safety and effectiveness are still under study.\textsuperscript{[49]}

**Three-dimensional (3D) conformal external beam radiation therapy**

Three-dimensional (3D) conformal external beam radiation therapy uses standard external beam radiation to target only the tumor bed. Studies on 3D conformal external beam radiation therapy are limited at this time. Some early findings suggest the cosmetic look of the breast may be worse with 3D conformal external beam radiation therapy than with standard radiation therapy.\textsuperscript{[23]} In general, this therapy should only be given as part of a clinical trial. However, select women may be appropriate for treatment outside of a clinical trial.

**Intra-operative radiation therapy**

With intra-operative radiation therapy, a single dose of radiation is given to the tumor bed during lumpectomy. This dose of radiation is higher than in a standard radiation session. Some early findings suggest that intra-operative radiation therapy is less effective than standard radiation therapy at reducing rates of breast cancer recurrence. Intra-operative radiation therapy needs further study before its risks and benefits are fully known. At this time, it is being studied mainly in Europe.

**Emerging Areas in Metastatic Breast Cancer Treatment**

Many new treatments for metastatic breast cancer are under study. Most of these are drug therapies. Some focus on treating the whole body, while others focus on the breast, chest wall and nearby lymph nodes. Findings from clinical trials of these treatments will determine whether or not they become a part of standard care for metastatic breast cancer. Sometimes, these treatments go on to be part of early stage breast cancer care.\textsuperscript{[50]}

**Tyrosine kinase inhibitors**

Tyrosine kinase inhibitors are targeted therapies for cancer. Although some tyrosine kinase inhibitors are used to treat other types of cancer, lapatinib (Tykerb) is the only one FDA-approved for the treatment of breast cancer. Lapatinib is only used to treat HER2/neu-positive metastatic breast cancer. Other tyrosine kinase inhibitors are under study for use in the treatment of metastatic breast cancer.
PARP inhibitors
Poly(ADP-ribose) polymerase (PARP) inhibitors are a class of drugs under study for many types of cancer, including breast cancer. PARP is an enzyme involved in DNA repair. At this time, PARP inhibitors are only offered in clinical trials for people with metastatic breast cancer. Early findings suggest PARP inhibitors hold the most promise for people with metastatic breast cancer who have a BRCA1 or BRCA2 gene mutation.

Cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors
CDK4 and CDK6 are enzymes important in cell division. CDK4/6 inhibitors are a new class of drugs designed to interrupt the growth of cancer cells. CDK4/6 inhibitors in combination with hormone therapy are under study for the treatment of hormone receptor-positive metastatic breast cancer.

PI3 kinase inhibitors
PI3 kinase is an enzyme important in cell growth. The PIK3CA gene helps control PI3 kinase enzyme activity. Some breast cancers have a mutation in the PIK3CA gene (this gene mutation is in the genes of breast cancer, not the person). This mutation can affect PI3 kinase and cause the tumor to grow. PI3 kinase inhibitors are a new class of drugs designed to interrupt PI3 kinase signals and stop the growth of cancer cells. PI3 kinase inhibitors are under study for the treatment of metastatic breast cancer.

Bevacizumab (Avastin) and other anti-angiogenesis drugs
Anti-angiogenesis drugs, such as bevacizumab (Avastin), block the growth of new blood vessels (angiogenesis). Without a blood supply, the cancer cannot grow. Although early data found bevacizumab offered benefit to some women with metastatic breast cancer, longer-term follow-up data did not confirm these findings. In 2011, the FDA withdrew its approval for the use of bevacizumab in the treatment of metastatic breast cancer. However, bevacizumab and other anti-angiogenesis are still under study for the treatment of metastatic breast cancer. Bevacizumab is still FDA-approved for use in other cancers.

REFERENCES


