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An overview of Breast cancer treatment

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Mini Review

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What is breast cancer?

Breast cancer is a malignant tumor [1] that initiates in the breast cells and tissues. A malignant tumor is a group of cancer cells that can develop and invade the surrounding tissues or even spread (metastasize) to different areas of the body. The disease occurs mostly only in women, but men are also rarely noticed [2].

To understand the treatment for breast cancer, we need to have some basic information and knowledge about the normal structure of the breast [2-5] The female breast is made up of lobules (milk-producing glands), *ducts* (tiny tubes that carry the milk from the lobules to the nipple), and *stroma* (fatty tissue and connective tissue surrounding the ducts and lobules, blood vessels, and lymphatic vessels).

Most often tumors of breast begin in the cells that adhere the ducts (*ductal* cancers). Some begin in the cells that line the lobules (*lobular* cancers), while a small number occur in other tissues.

Types of breast cancers

Breast cancer can be divided into the following types [6-9] depending on how the cancer cells appear when observed under the microscope.

Most of the breast cancers are *carcinomas*, and is one of the types of cancer that initiates in the epithelial cells (that line organs and tissues) like the breast. In fact, breast cancers are a type of carcinoma called *adenocarcinoma*, [10-14] which starts in the glandular tissue. Other types of cancers can also occur in the breast such as sarcomas [15], which gets initiated in the cells of muscle, fat, or connective tissue.

A single breast tumor can be a combination of different types in some cases or be a mixture of invasive [16] and in situ cancer. And in some minor cases of breast cancer, the cancer cells may not lead to tumor.

Based on proteins in or on the cancer cells it can also be classified into two groups like hormone receptor-positive or triple-negative [17].

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Signs and symptoms of breast cancer

In most cases breast cancer is first observed as a new lump or mass. A painless and hard mass that has irregular edges is more likely to be cancerous, but breast cancers can also be tender, soft, or rounded and even painful in few cases. Hence, it is important to be checked by a health care professional experienced in diagnosing breast diseases if any new breast mass or lump or breast change is observed. Sometimes a breast cancer can also spread to the lymph nodes [18-20] under the arm or around the collar bone and cause a swelling or lump in that area before the original tumor is large enough to be felt in the breast tissue.

Other symptoms [21] of breast cancer include:

- Swelling of all or part of a breast
- Skin irritation
- Skin dimpling
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness or thickening of the nipple or breast skin
- Nipple discharge (other than breast milk)

How is breast cancer diagnosed?

Breast cancer is mostly noticed after the symptoms appear, but many women experience no symptoms with early breast cancer. This is the reason the physicians recommend few screening tests before any symptoms develop which is very important and should never be ignored.

If anything suspicious is observed during the initial and primary screening exam [22], or if the victim is observed to have any symptoms of breast cancer described in the previous section, the physician would use one or more methods to find out if the disease is present. If cancer is found, then the other tests have to be continued to determine the stage of the cancer.

Medical history and physical exam

If you think you have observed any signs or symptoms that might be experienced as breast cancer, then sure you need to consult the doctor as soon as possible. Your doctor would initially ask you questions about your symptoms regarding your medical history [23] any other health problems, and possible risk factors [24,25] for benign breast conditions or breast cancer which would provide them a primary opinion based on the report given.

Then breasts will be thoroughly examined for any lumps or suspicious areas and accordingly as per the symptoms their texture, size, and relationship to the skin and chest muscles is examined. Any changes in the nipples or the skin of your breasts would be noted. The lymph nodes in your armpit and above your collarbones [26] may be palpated (felt), because enlargement or firmness of these lymph nodes might indicate spread of breast cancer. Then doctor would also do a complete physical exam to judge your general health and whether there is any evidence of cancer that may have spread. If the doctor would find the primary test a bit positive noticing any breast symptoms and the report if suggest breast cancer might be present, more tests would probably be done. These might include imaging tests, looking at samples of nipple discharge, or doing biopsies of suspicious areas.

Imaging tests used to evaluate breast disease

Imaging tests used to evaluate the cancer in the body are x-rays, magnetic fields, sound waves, or radioactive substances which would create pictures of the inside of your body. Imaging tests [27] may be

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done for various number of reasons, sometimes even 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 and the progress of the treatment.

Mammograms

A mammogram [28-30] is an x-ray report of the breast. Screening mammograms are done 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 and consider the report of those two views for an initial confirmation of the cancer.

Breast ultrasound

Ultrasound, also known as *sonography*, [31] uses sound waves to examine and diagnose a part of the body. This test includes a small microphone-like instrument called a *transducer* which 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 the body tissues [32-35]. The echoes emitted are then 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 any kind of radiation.

Magnetic resonance imaging (MRI) of the breast

MRI scans [36] use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a specific pattern by the type of body tissue and this pattern would be unique when observed by certain diseases. A computer then translates the pattern into a very detailed image from which a conclusion is drawn for the treatment of the cancer observed. A contrast liquid called *gadolinium* is injected into a vein before or during the scan to get the details better for the MRI scans [37-39].

Treatment of Breast Cancer

There are different approaches suggested by the physician based on the stage of the cancer observed and diagnosed in the person. The article provides a short description of most of the treatments encountered and observed for the Breast cancer.

Surgery for breast cancer

Most women with breast cancer have some type of surgery. Surgery [40] is often needed to remove the breast tumor. Among them different approaches include breast-conserving surgery and mastectomy. The breast can be reconstructed at the same time along with the surgery or even later on as suggested by the doctor and opinion of the victim. Surgery also helps to check and examine the lymph nodes under the arm for the spread of the cancer. And this surgery includes the two types, a sentinel lymph node biopsy [41] and an axillary (armpit) lymph node dissection.

Breast-conserving surgery

This type of surgery is sometimes referred to as partial or segmental mastectomy. It is also sometimes called as lumpectomy [42] or quadrantectomy. In breast-conserving surgery, only the part of the breast affected with the cancer and containing the cancer is removed off. The aim of this method is to remove the cancer and even some surrounding normal tissue. The size and location of the tumor and other factors would provide an idea about how much part of the Breast is removed.

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Mastectomy

In Mastectomy [43] surgery the entire breast is removed. Sometimes along with the entire breast nearby surrounding tissue is also removed off depending on the cancer spread in the tissue.

Radiation therapy for breast cancer

Radiation therapy includes the treatment with high-energy rays [44-46] which would help to damage and destroy the cancer cells. After the breast-conserving surgery is done then the radiation to the breast is given to reduce the chance that the cancer would revert back in the breast or the surrounding lymph nodes. In some cases radiation may also be suggested after mastectomy based on the cancer size, patients either with a cancer larger than 5 cm or even when the cancer is noticed in the lymph nodes.

In few cases the cancer is also spread to other areas of the body like bones, Brain in these situations also radiation therapy is recommended and treatment is provided. Radiation therapy can be given externally [47] (external beam radiation) or internally (brachytherapy) [48].

Chemotherapy for breast cancer

Chemotherapy is treatment which includes cancer-killing drugs that may be given intravenously (injected into a vein) or orally [49-52]. The drugs reach the cancer cells in most parts of the body by travelling through the bloodstream. Chemotherapy is suggested to take in specific cycles and in combinations for effective treatment, with each cycle of treatment followed by a recovery period. And Chemotherapy treatment usually lasts for several months with strict regimens provided.

In most cases like in adjuvant and neoadjuvant treatment, chemotherapy is more effective when combinations of more than one drug are used for treatment. Till now different combinations have been tried but there is no particular evidence reported that these drug are the best combination. The most widely used and prescribed chemotherapy drugs used for early breast cancer are the anthracyclines [53] like doxorubicin and epirubicin and the taxanes [54] like paclitaxel and docetaxel. Fluorouracil (5-FU) [55], cyclophosphamide Cytoxan and carboplatin are also given along the above mentioned combination of drugs for effective treatment.

In HER2 positive cancers, the targeted drug trastuzumab (Herceptin) [56] is given with any one of the taxanes. Pertuzumab (Perjeta) can also be combined with trastuzumab and docetaxel for HER2 positive cancers [57] for effective treatment and based on the cancer spread in the victim.

Hormone therapy for breast cancer

Hormone therapy [58] is another kind of systemic therapy. Hormone therapy more helps an an adjuvant therapy after surgery, to help reduce the risk of it's revert back but it can be used as neoadjuvant treatment. It is also used to treat cancer that might be noticed after treatment or has spread.

Estrogen promotes the growth of cancers that are hormone receptor-positive. And about 2 out of 3 of breast cancers are reported to be hormone receptor-positive which contain receptors for the hormones estrogen (ER-positive cancers) [59] and/or progesterone (PR-positive cancers). Most types of hormone therapy for breast cancer works by either lowering the estrogen levels or by stopping the estrogen from acting on the breast cancer cells. Therefore this kind of treatment is helpful for hormone receptor-positive breast cancers, but it does not help patients whose tumors are hormone receptor negative (both ER- and PR-negative).

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Tamoxifen [60] blocks the estrogen receptors in the breast cancer cells there by preventing the estrogen from binding to them and hence the cells do not grow and divide. While tamoxifen acts like an anti-estrogen in breast cells, it acts like the estrogen in other organs like the uterus and the bones. Because it acts like estrogen in some tissues but like an anti-estrogen in others, it is called a *selective estrogen receptor modulator* or SERM. Toremifene is a drug similar to tamoxifen. It is also a SERM and functions in the same mechanism of Tamoxifen and also reported to have similar side effects. Therefore it is approved only to treat metastatic breast cancer. This drug is not likely to work if tamoxifen has been used and stopped working as tolerance to the drug might be developed during the treatment with tamoxifen. Fulvestrant [61] is a drug that first blocks the estrogen receptor and then also eliminates it temporarily and it acts like an anti-estrogen throughout the body and is not a SERM.

Aromatase inhibitors (AIs) [62]: These drugs stop estrogen production in post-menopausal women to treat both early and advanced breast cancer. Three drugs have been reported by functioning in this mechanism: letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). They work by blocking an enzyme (aromatase) in fat tissue which is responsible for making small amounts of estrogen in post-menopausal women [63]. They are only effective in women whose ovaries aren't working either due to menopause or due to treatment with luteinizing hormone-releasing hormone analogs as they cannot stop the ovaries from making estrogen.

Targeted therapy for breast cancer

These targeted drugs work by different mechanism from standard chemotherapy drugs. They often produce certain side effects but are less severe [64]. In about 1 in 5 patients with breast cancer, the cancer cells are reported to be noticed with some growth-promoting protein known as HER2/neu (or just HER2) on their surface. Breast cancers noticed with high amount of this protein tend to grow and spread more aggressively without special treatment. To target this protein and prevent the spread of breast cancer a number of drugs have been provided.

They include Trastuzumab and pertuzumab [65] which are man-made monoclonal antibody versions of a very specific immune system protein. They are given through IV route.

Ado-trastuzumab emtansine is a monoclonal antibody attached to a chemotherapy drug. It is also given intravenouly. Lapatinib [66] is another targeted drug that is not an antibody and is given as a pill.

Bevacizumab (Avastin) is an example of anti-angiogenesis drug. Although bevacizumab [67-70] is reported to be very helpful in the treatment of advanced breast cancer, this approach still may prove not very remarkable in breast cancer treatment. Manyother anti-angiogenesis drugs are being tested in clinical trials and are yet to be implemented.

Other targeted drugs: Everolimus (Afinitor) is another targeted therapy drug that was reported to help to improve the working of hormone therapy drugs. It is advised and approved to be given with exemestane (Aromasin) [71]to treat advanced hormone receptor-positive breast cancer in post-menopausal women. It has also been studied for treatment of earlier stage breast cancer andwith other hormone therapy drugs. In a case study, letrozole plus everolimus showed better effect than letrozole [72] alone in shrinking and reducing the breast tumors before surgery. It also seemed to help in treating advanced hormone receptor-positive breast cancer when added to tamoxifen. Everolimus when used in combination with chemotherapy and the targeted drug trastuzumab has provided good results and this is still under clinical study. Other drugs like everolimus are also being studied.

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Bone-directed therapy for breast cancer

When cancer spreads to bones, it causes pain and also leads to bones breaking (fractures) and other problems. Drugs like bisphosphonates [73-76] and denosumab can lower the risk of these problems. Bisphosphonates are drugs that help strengthen bones and reduce the risk of fractures and pain in bones that have been weakened by metastatic breast cancer. Pamidronate [77-80] (Aredia) and zoledronic acid (Zometa) are few examples that help to reduce the risk of bone fractures due to breast cancer spread to bones. They are given through IV route. Denosumab (Xgeva, Prolia) [81-84] is another drug that can help reduce the risk of problems from breast cancer metastasis to the bone. It works differently from bisphosphonates.

Abraxane and Albumin-Bound Nanoparticle Drugs

Abraxane is a new drug reported to help breast cancer. A process called protein-bound nanoparticle technology creates tiny particles that bind the paclitaxel [85-88] to a naturally occurring protein called albumin. This binding makes little packets of paclitaxel which are as little as bubbles that can be dissolved in water. This means no more solvent which in turn requires no more medications before chemotherapy [89-92] and no more side effects along with them.

New Advancements in treatment of Breast cancer

As breast cancer has been reported statically [93-99] a wide spread problem all over the world due to its high prevalence many researches are being carried out to report different trends and improve the treatment of Breast cancer. New treatments for breast cancer are years away from regular treatment regimens.

One among the emerging new treatments are anti-angiogenesis [100] drugs. They work by blocking the formation of new blood vessels that feed tumors and help them grow. These drugs have different mechanism of action as they block the bloodvessels [101-104] that feed the new cancer cells forming and has been proved to show promising results in treating colon cancer and are now being studied in patients with advanced breast cancer.

Even so, new breast cancer treatments are available now. Over the past year, Physicians have learned a lot more about many targeted therapies and chemotherapies that very soon may be helping millions of women live longer and healthier lives after they have reported to have breast cancer.

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