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R E V I E W A R T I C L E

Review on Diagnosis and Treatment of Breast Cancer

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A B S T R A C T

Breast cancer is the most common cause of cancer-related deaths in women and occurs most frequently in postmenopausal women over the age of 50. Breast cancer also occurs in men but is very rare, making up around 1% of all breast cancer cases. The most common symptoms of breast cancer are changes in the breasts such as the presence of a lump, changes to the nipple, discharge from the nipple or changes in the skin of the breast. Initial investigations for breast cancer begin with a physical examination, mammography and ultrasound scan. In some cases, breast magnetic resonance imaging (MRI) will also be performed. If a tumour is found, a biopsy will be taken to assess the cancer before any treatment is planned. The treatment of breast cancer depends on how far advanced the cancer is (Stage 0 IV) and what type of cancer is present. Surgery, radiotherapy, chemotherapy, endocrine therapy and targeted therapy are used in the treatment of breast cancer. The presence of biomarkers including hormone receptors and a receptor called HER2 also help to determine what type of therapy is given.

Keywords: Breast cancer, Tumour, Women, Nipple, Surgery, Chemotherapy.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Breast cancer is the most common female cancer in the world with an estimated 1.67 million new cancer cases diagnosed in 2012. While the age adjusted incidence rates of breast cancer in India is lower than the western countries, because of the large population the burden of breast cancer is high. With an annual incidence of approximately 1,44,000 new cases of breast cancers in India, it has now become the most common female cancer in urban India[1]. In India the incidence of breast cancer is significantly lower than western countries. Breast cancer in India varies from as low as 5 per 100,000 female population per year in rural areas to 30 per 100,000 female

population per year in urban areas. There is an impression of higher incidence of breast cancer in younger women in India as most hospital based series report median age of breast cancer patients a decade younger than western series. However this may be due to a combination of the population structure and inherent bias against referral, treatment and ascertainment of breast cancer in the elderly in India rather than a true reflection. The incidence of breast cancer increases with age and this is true in India like rest of the world[2]. With the exception of 5-10% breast cancers where the main risk factor is genetic predisposition, in the remaining 90% of sporadic breast cancers, the identified risk factors are either reproductive, lifestyle or environmental factors, primarily through their influence on the hormonal milieu. No breast cancer risk factor, unique to the Indian population has been widely reported. Breast cancer screening using various approaches has been the subject of several large randomized trials in USA, Canada and Europe. Population-based mammographic screening of asymptomatic postmenopausal women has shown a modest reduction in breast cancer deaths in high incidence affluent western countries but with associated over diagnosis and overtreatment[3].

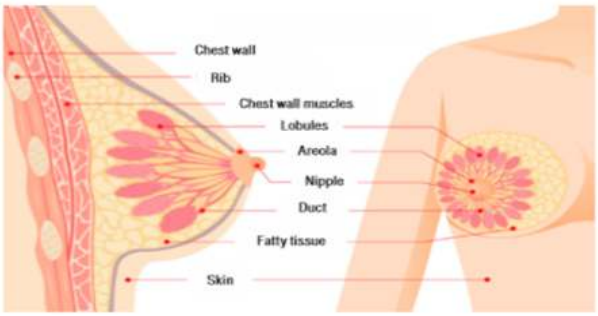

Fig 1: Anatomy of the Female breast

Types of Breast Cancer

Breast cancer can be categorised by whether it is non-invasive or invasive.

Non-invasive breast cancer (in situ):

Ductal carcinoma in situ (DCIS) is a pre-malignant lesion – it is not yet cancer, but can progress to become an invasive form of breast cancer. In this type of cancer, the cancer cells are in the ducts of the breast but have not spread into the healthy breast tissue. Lobular neoplasia (previously called lobular carcinoma in situ) is when there are changes in the cells lining the lobules, which indicate that there is an increased risk of developing breast cancer in the future. Lobular neoplasia is not actually breast cancer, and although women with lobular neoplasia will have regular check-ups, most will not develop breast cancer[4].

Invasive breast cancer:

Invasive breast cancer is the name given to a cancer that has spread outside the ducts (invasive ductal breast cancer) or lobules (invasive lobular breast cancer). These can be further classified by their histology; for example, tubular, mucinous, medullary and papillary breast tumours are rarer subtypes of breast cancer[5]. Breast cancer is also categorized by how advanced the disease is:

Early breast cancer:

Breast cancer is described as early if the tumour has not spread beyond the breast or axillary lymph nodes (also known as Stage 0 IIA breast cancer). These cancers are usually operable and the primary treatment is often surgery to remove the cancer, although many patients also have preoperative neoadjuvant systemic therapy.

Locally-advanced breast cancer:

Breast cancer is locally-advanced if it has spread from the breast to nearby tissue or lymph nodes (Stage IIB III). In the vast majority of patients, treatment for locally-advanced breast cancer starts with systemic therapies. Depending on how far the cancer has spread, locally-advanced tumours may be either operable or inoperable (in which case surgery may still be performed if the tumour shrinks after systemic treatment)[6].

Metastatic breast cancer:

Breast cancer is described as metastatic when it has spread to other parts of the body, such as the bones, liver or lungs (also called Stage IV). Tumours at distant sites are called metastases. Metastatic breast cancer is not curable but is treatable.

Advanced breast cancer: Advanced breast cancer is a term used to describe both locally-advanced inoperable breast cancer and metastatic breast cancer[7].

Subtypes based on hormone receptor status and HER2 gene expression:

The growth of some tumours is stimulated by the hormones oestrogen and progesterone. It is important to find out whether a tumour is oestrogen receptor (ER) or progesterone receptor (PgR) positive or negative, as tumours with a high level of hormone receptors can be treated with drugs that reduce the supply of hormone to the tumour. HER2 is also a receptor that is involved in the growth of cells and is present in about 20% of breast cancers. Tumours that have a high level of HER2 can be treated with anti-HER2 drugs. Tumours that don't have ER, PgR or high levels of HER2 are described as triple-negative tumours. Tumours can be classified into subtypes based on hormonal and HER2 receptor status as follows: luminal A-like (ER and PgR positive, HER2 negative tumours), luminal B-like (ER and/or PgR positive, HER2 positive or negative tumours), HER2 overexpressing (ER and PgR negative, HER2 positive tumours) and basal-like (triple-negative tumours). Further information regarding the impact of these subtypes on breast cancer treatment will be explained later in this guide in the section. How will my treatment be determined[8].

Symptoms of breast cancer

Symptoms of breast cancer include:

- A lump in the breast
- Change in the size or shape of the breast
- Dimpling of the skin or thickening in the breast tissue
- An inverted nipple
- Rash on the nipple
- Discharge from the nipple

- Swelling or a lump in the armpit
- Pain or discomfort in the breast that doesn't go away
- Skin redness
- Skin thickening

You should see your doctor if you experience any of these symptoms. However, it is important to remember that these symptoms may also be caused by other conditions. Certain symptoms may indicate the presence of metastases – for example, a lump or swelling under the armpit, in the breast bone or collar bone area may be a symptom of lymph node metastases. Pain in a bone or a bone prone to fracture might suggest bone metastases, and lung metastases may cause symptoms of ongoing chest infections, persistent cough and breathlessness. It's important not to be alarmed by these symptoms as they don't necessarily mean that you have metastases; however, you should discuss any concerns with your doctor.

2. Diagnosis

Breast cancer is usually diagnosed by clinical examination, imaging and biopsy.

Clinical examination:

Your doctor will examine your breasts and lymph nodes. He/she will also ask you about any family history of breast cancer and whether you have reached menopause or not. He/she may also take a blood sample for routine blood tests. If there is a suspicion that you may have a breast tumour, he/she may arrange for you to have an imaging scan[9].

Imaging:

Imaging techniques used for women in whom breast cancer is suspected include mammography, ultrasound and/or MRI scan:

Mammography: Mammography is a type of low-dose x-ray that looks for early breast cancers. Your breasts will each be placed on the x-ray machine and pressed between two plates to produce a clear image. If the mammography screening shows anything suspicious in your breast tissue, your doctor will investigate further.

Ultrasound scan:

Ultrasound uses high frequency sound waves to create an image of the inside of your body. In investigations for breast cancer, a hand-held ultrasound device lets the doctor examine your breasts and the lymph nodes in your armpit. The ultrasound can show whether a lump is solid or is a fluid-filled cyst[10].

MRI scan:

MRI uses magnetic fields and radio waves to produce detailed images of the inside of your body. An MRI scanner is usually a large tube that contains powerful magnets. You lie inside the tube during the scan, which takes 15–90 minutes. Although these are not used as part of routine investigations, an MRI scan might be used in certain circumstances, for example in patients with a family history of breast cancer, BRCA mutations, breast implants, lobular cancers, if there is a suspicion of multiple tumours, or if the results of other imaging techniques are inconclusive. MRI is also used to see if a tumour has responded to treatment, and to plan further therapy[11].

Biopsy:

When breast cancer is suspected, a biopsy is taken from the tumour before any treatment is planned. The biopsy is taken with a needle, usually guided by ultrasound (or sometimes using mammography or MRI, if the tumour is not visible on ultrasound) to make sure the biopsy is taken from the correct area in the breast. The biopsy gives the doctors important information on the type of breast cancer. At the same time as the biopsy, a marker may be placed into the tumour to help surgeons remove the whole tumour at a later date.

3. Treatment

Your treatment will depend upon the size, location and number of tumours and the pathology (subtype, grade and presence of biomarkers) of the tumour, as well as your age and general health. The choice and combination of treatments will be discussed with you and your preferences will be taken into account. One of the most important decisions you will have to make is where to be treated. Treatment within a multidisciplinary and specialized team improves survival and quality of life, as opposed to being treated by a single doctor. All of your treatment decisions should be taken after discussion in a multidisciplinary meeting, where doctors from different specialties, nurses and other health professionals involved in your care will discuss your case and decide which treatment is the best option for you[12].

Surgery:

The two types of surgery for breast cancer are breastconserving surgery, in which the surgical team removes the tumour but tries to keep as much of the breast as possible, or mastectomy, in which the whole breast is removed. If the lymph nodes in your armpit look like they are clear of cancer in imaging tests, then a technique called sentinel lymph node biopsy should be performed. This identifies the most important (sentinel) lymph node and examines it; if no cancer is detected, then no other lymph nodes will be removed, but if cancer is found in that lymph node, more nodes may have to be removed (called axillary dissection). Patients undergoing mastectomy should usually be offered immediate or delayed breast reconstruction, except in the case of inflammatory breast cancer[13].

Radiotherapy:

Radiotherapy is a type of treatment that uses ionizing radiation, which damages the DNA of cancerous cells, causing the cells to die. Radiotherapy is usually given after breast-conserving surgery and may also be given after mastectomy. Radiotherapy may also be given to patients with locally-advanced disease which remains inoperable after systemic treatment and may be considered in certain patients with metastatic disease to treat the symptoms of the primary tumour or distant metastases and improve quality of life. Radiotherapy after breast-conserving surgery is usually given as whole breast radiotherapy (WBRT). In patients considered to be at high risk of recurrence who have already undergone WBRT, a radiotherapy 'boost' may be given this is an extra, lower dose of radiation directed specifically to the area that the tumour was removed from. This may be done similarly to WBRT with external radiotherapy or with

brachytherapy, in which a radiation source is placed into the breast tissue for a short time to provide internal radiotherapy focused only on a small margin of tissue surrounding the site of surgery[14].

Patients who are considered to be at a low risk of recurrence may instead receive a short course of radiotherapy using a technique called accelerated partial breast irradiation. This treatment is shorter than WBRT and reduces the exposure of healthy breast tissue and other organs in the chest (e.g. heart, lungs) to radiation, reducing the risk of long-term side effects. Some patients also require radiotherapy after mastectomy, because of the presence of factors that increase the risk of the cancer coming back. This is done similarly to radiotherapy after breast-conserving surgery.

Estrogen Receptor-Positive Therapies:

Women with breast cancer who test positive for hormone receptors are candidates for treatment with hormone therapy to reduce the likelihood of recurrence or as a core component of treatment for advanced disease. Currently available endocrine strategies for the treatment of estrogen receptor- (ER) positive breast cancer include targeting the ER with the anti-estrogen drug tamoxifen. Another option is suppressing the amount of available ligand (estrogen) for the receptor either with gonadal suppression in pre-menopausal oophorectomy, or luteinizing hormone-releasing hormone agonists, or with the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole in postmenopausal women and by downregulating the receptor with fulvestrant. Given their proven efficacy and generally favorable adverse effect (AE) profile, these endocrine therapies are widely used in the treatment of both earlystage and recurrent and/or metastatic breast cancer[15].

Systemic therapy:

There are several types of systemic therapy that you may be treated with, depending on the type and stage of cancer you have.

Chemotherapy:

Chemotherapy destroys cancer cells and is used to treat most triple negative, HER2 positive and luminal B-like breast cancers. Chemotherapy is usually given every 1–3 weeks as intravenous infusions. Some patients may also be offered additional oral chemotherapy following completion of standard intravenous chemotherapy.

Endocrine therapies:

Endocrine therapies aim to reduce the effects of oestrogen in ER positive breast cancers. This is the most important type of systemic treatment for ER positive tumours, also called hormone-dependent tumours[16]. There are a number of types of endocrine therapy available, which are taken orally or administered as an injection:

- Selective oestrogen receptor modulators (SERMs) block ER on breast cells to prevent oestrogen attaching to the receptors. Tamoxifen is a type of SERM.
- Selective oestrogen receptor down regulators (SERDs), such as fulvestrant, work in a similar way to SERMs, but also reduce the number of ERs.
- Ovarian function suppression by gonadotropin-releasing hormone analogues or by surgery may be offered to pre- and perimenopausal women to reduce the supply of oestrogen from the ovaries to the tumour.
- Aromatase inhibitors reduce the production of oestrogen in tissues and organs other than the ovaries, and is therefore effective only in postmenopausal women, unless the function of the ovaries is suppressed (oestrogen levels are artificially lowered) in premenopausal women. Anastrozole, letrozole and exemestane are all aromatase inhibitors[17].

Targeted therapy:

Targeted therapies are drugs that block specific signaling pathways in cancer cells that encourage them to grow. A number of targeted therapies are used in the treatment of breast cancer:

- ✓ Anti-HER2 agents act on the HER2 receptor to block signalling and reduce cell proliferation in HER2 positive breast cancers. Trastuzumab, lapatinib, pertuzumab and trastuzumab emtansine (TDM-1) are all currently-used anti-HER2 agents. Neratinib is a new anti-HER2 agent that may also be used to treat HER2 positive disease.
- ✓ Inhibitors of cyclin-dependent kinases 4/6 (CDK4/6) reduce cellular proliferation in tumours. Palbociclib, ribociclib and abemaciclib are CDK4/6 inhibitors used in the treatment of breast cancer.
- ✓ Inhibitors of mechanistic target of rapamycin (mTOR), such as everolimus, reduce the growth and proliferation of tumour cells stimulated by mTOR signalling.
- ✓ Inhibitors of poly ADP-ribose polymerase (PARP) make it difficult for cancer cells to fix damaged DNA, which can cause cancer cells to die. Olaparib and talazoparib are new PARP inhibitors that may be used to treat some patients with a BRCA mutation.
- ✓ Vascular endothelial growth factor (VEGF) inhibitors, such as bevacizumab, stop tumours from stimulating blood vessel growth within the tumour, thereby starving them of the oxygen and nutrients they need to continue growing[18].

Advanced approaches for management of breast cancer

Gene Therapy:

It is generally accepted that cancer arises because of an accumulation of multiple molecular genetic defects that culminate in a cellular phenotype characterized by unregulated growth. Based on the knowledge, a variety of gene therapy strategies have been developed as potential new therapies for cancer. Current knowledge of proto-oncogene and tumor suppresser genes in the genesis of malignancy has stimulated the development of gene therapy tactics directed at ablating or restoring such genes, respectively. In other strategies, cancer cells are endowed with the ability to convert a systemically delivered prod rug to a toxic metabolite, or a target for destruction by replicating viral vectorsconversely transfer of drug resistance genes into normal cells may provide chemo protection during high dose antineoplastic treatment. Finally, immune system modulation can activate anticancer drug defense mechanisms[19].

Oncogenes:

Inactivation Several oncogenic proteins have been identified and associated with various malignancies. The most commonly applied approach in clinical trials to date has been use of antisense strategies. Transcription of oncogenes also can be inhibited by using adenoviral gene E1A, which interfere with the transcription of erbB-2, a strategy useful in treating cancer that over express this oncogenic protein, such as breast and ovarian cancer[20].

Augmentation of Tumor Suppresser Genes:

More than 24 tumor suppresser genes have been identified, and mutations in these genes have been associated with a variety of neoplastic conditions. Several clinical trials are under way to deliver p53 using adenoviral vectors to a variety of cancers. Similarly, viral vectors have been utilized to introduce a retinoblastoma gene and breast cancer gene BRCA1 into bladder and ovarian cancer, respectively. In some situations, this approach will fail, because the mutant gene exhibits dominant negative effects on the normal gene. To circumvent this problem for p53 gene therapy, a genetic repair strategy rather than a gene augmentation approach could be more effective[21].

Cell-Target Suicide:

A conversion of a pro drug to a toxic metabolite by genetically engineering tumor cells is an attractive way to create an artificial difference between normal and neoplastic tissue. This can be achieved by the expression of a gene that confers a dominant, negatively selectable phenotype to the cancer cells, such as cell death imparted by expression of a prodrug – metabolism enzyme. Greater selectively in killing malignant cells will be obtained by transferring a gene that is not normally found inhuman beings (e.g. HSV--thymidine kinase), rather than by overexpression an endogenous gene. The prototype for this approach utilizes the HSV-1 Thymidine kinase gene given to combination with produg ganciclovir in a manner distant from mammalian thymidine kinase[22]. Phosphorylated ganciclovir is ultimately incorporated into DNA and inhibits DNA synthesis and transcription. The efficacy and safety on this approach is being tested in several clinical trials involving multiple malignancies.

Chemo protection Approach:

The MDR-1 gene encoding the multidrug therapy transporter protein (also known as P- glycoprotein) has received much attention in this regard. This trans membrane protein transports a wide variety of chemotherapeutic agents (e.g. doxorubicin, vinca alkaloids, epipodophyllotoxins and paclitaxel) and other drugs out of cells, thus protecting them from the agents' toxic effects.

Virus-mediated oncolysis:

Certain viruses, including adenovirus, and HSV-1 can infect the lyse tumor cells. The use of oncolytic virus in combination with other gene based antineoplastic strategies has emerged as a promising addition to the multidimensional treatment cancers. Selective replication of virus in tumor cells leads to the cell lysis and to local dissemination of infective viral progeny to neighboring cancers cells. Most investigational uses of this strategy have utilized replication-competent adenovirus and HSV-1[23].

Immunomodulation:

Various cytokines can enhance immunity against cancer cells, and this observation has stimulated the development of gene- based approaches to modulate the immune reaction in malignancy.

Ectopic Cytokine Expression:

A variety of cytokine have been shown to decrease tumor growth when ectopically expressed in tumor cells or in there microenvironment. Some immune stimulatory agents do not alter the growth rate of the tumor initially, but lead to immunity against tumor growth if the animal is later challenged with wild type tumor cells.

Immune enhancement:

One such approach is to express on the surface of cancer cells highly immunogenic molecule, such as all type MHC antigens. It has been long known those additional "costimulatory" pathways distinct from the T-cell are needed to achieve T cell activation. The molecules B7-1 (CD 80) and B7-2 (CD 86) stimulate one such pathway. The B7s, whose expression normally is limited to antigen presenting cells and other specialized immune effector cells, engage specific receptors on the T cells surface in concert with antigen binding to the T-cell receptor[24].

4. Conclusion

Breast cancer is the most common cancer in women worldwide. In 2011, an estimated 230,000 women were diagnosed with breast cancer in the U.S. alone, with an estimated 40,000 deaths, making it the second most common cause of cancer related death in women.Most women with breast cancer will have some type of surgery to remove the tumor. Initial investigations for breast cancer begin with a physical examination, mammography and ultrasound scan. In some cases, breast magnetic resonance imaging (MRI) will also be performed. If a tumour is found, a biopsy will be taken to assess the cancer before any treatment is planned.Depending on the type of breast cancer and how advanced it is, you might need other types of treatment as well, either before or after surgery, or sometimes both.The mainstays of breast cancer treatment are surgery, radiation, chemotherapy, hormone therapy, and targeted therapy. But scientists continue to study novel treatments and drugs, along with new combinations of existing treatments.

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