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AN UPDATED OVERVIEW ON BREAST CANCER

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ABSTRACT

Breast cancer is that the most typically occurring cancer in women and also the second most common overall. There have been over a pair of million new cases in 2018. This review briefly explain the importance of DNA damage and repair, introduce the current classification schemes for breast cancer, and review the known defects in the repair machinery that have been associated with the risk of breast cancer, stages, diagnosis of breast cancer and current therapies of the breast cancer. Finally, we discuss how the understanding of these pathways can help to design therapeutics for specific targeting of breast cancer tumors, stages, diagnosis of breast tumors, risk factors and recent therapies of the breast cancer. More importantly, their implications for future study are also evaluated and potential targeted strategies are proposed to break through the limitation of current therapies.

KEYWORDS: Breast cancer, stages, BRCA gene mutation, diagnosis, treatment.

INTRODUCTION

Cancer, one of the most life-threatening diseases, has more than 200 distinct types associated with it, affecting over 60 human organs. More than 90% of all cancer-related deaths occur from metastasis of the primary cancer tumor.[1] Breast cancer is that the most typically occurring cancer in women and also the second commonest cancer overall. There have been over a pair of million new cases in 2018.[2] National Cancer Institute has estimated that the diagnosis of 246,660 new cases and 40,450 deaths from this disease in the United States, and the incidence is still rising. Breast cancer is an increasingly serious health problem

all over the world, and its incidence and resistance to treatment are increasing significantly.[3] It conveys how much cancer is present, where it is located, and highlights important tumor characteristics. It also allows for efficient communication between clinicians and provides a framework for assessing and relaying prognostic information based on the sum of the tumor and disease features. In addition to its patient-specific purpose, it also forms the foundation on which changes in population-level cancer incidences can be more thoroughly and accurately evaluated, by allowing assessment of the overall impact of novel or changing breast cancer treatments.[4]

To achieve these goals, the American Joint Committee on Cancer (AJCC) was organized in 1959 to develop a system of cancer staging using standardized language acceptable to the American medical profession. The guiding philosophy was to develop a classification system that would convey the progression of the usual events that created the life history of a cancer, including tumor growth (size) and spread (to regional lymph nodes and/or distant organs).[5] The AJCC used the principles of the TNM system T indicates the tumor; N indicate the nodes; M. indicates the metastasis), as described by the International Union Against Cancer (UICC).[6]

In today's era of personalized medicine, breast cancer treatment is leading the charge to incorporate more patient-specific and tumor specific data into determining a patient's prognosis and thus customizing treatment decisions.[6]

Stages of the breast cancer

Grouping cancer cases into stages was derived from survival rates being higher for localized disease compared with those in which the disease had spread beyond the original site, initially referred to as early and late cases. Determining a patient's breast cancer stage typically starts with a physical examination to provide an initial evaluation of the extent of the cancer, such as the tumor location, tumor size, and presence of regional and/or distant metastases may be identified.[7]

Stage 0: 0 stage carcinoma ductal cancer in situ could be a non invasive cancer wherever abnormal cells are found within the lining of the breast milk duct. This stage atypical cell havn't unfolded outside of the ducts or lobules into the encompassing breast tissue.[8]

Stage 1: Clinical staging relies on the physical examination, imaging tests, and biopsies of affected areas. This designation is recorded with a lower case "c" before the TNM staging categories.

Stage 2: Pathologic staging can only be determined after a patient has had surgery to remove the primary tumor and regional lymph nodes. These results are then combined with the clinical stage to determine the final pathologic stage. This designation is recorded with a lower case "p" before the TNM staging categories.

Stage 3: Post-therapy or post neo-adjuvant therapy staging determines how much cancer remains after a patient completes preoperative systemic therapy and/or radiation therapy before surgery. This is often assessed after surgery, but it may incorporate both clinical and pathologic staging information. This designation is recorded with a lower case "y" before the TNM staging categories.

Stage 4-Restaging is performed if a cancer returns after treatment and is used to determine the extent of disease recurrence. However, importantly, the formal stage of a cancer does not change over time, even if the cancer returns or progresses. Rarely, a cancer may be restaged after a significant disease-free interval, which would include the same assessments performed at the time of the initial diagnosis and the new stage is recorded with a lower case "r" before the restaged TNM designation. A contralateral cancer is staged as a new episode of cancer, with the exception of direct tumor extension or dissemination via lymphatic spread.[4]

Mechanism of breast cancer

The molecular subtypes of breast cancer, which are based on the presence or absence of hormone receptors. The hormone receptors are estrogen(ER), progesterone(PR) and human epidermal growth factor receptor-2 (HER2), the hormone receptors include: The luminal A subtype is hormone receptor positive and HER2 negative(ER+, PR+, HER2−) hormone receptor positive and HER2 positive luminal B subtype (ER+, PR+, HER2− or HER2+). This classification allows ER+ tumor subtypes to be further stratified into luminal A and luminal B subtypes which have distinct clinical outcomes and impact differently on patient survival. Although the immune histochemistry of the normal-like subtype resembles that of luminal A tumors, it accounts for ~8% of all breast cancer cases in the LN-negative group and shares a similar tissue profile with normal breast.

Basal-like cancers are also called triple-negative hormone receptor negative and HER2 positive (HER2 positive), and hormone receptor negative andHER2 negative (ER−, PR−,

HER2−) and have an aggressive clinical outcome.Hormone receptor positive breast cancers area unit mostly driven by the steroid hormone pathway. In HER2 positive breast tumors, HER2 activates the PI3K/AKT and also the RAS/RAF/MAPK pathways, and stimulate cell growth, survival and differentiation.[9,10]

The oncogenes are FGFR1 (Fibroblast Growth Factor Receptor 1), PI3KCA (Phosphatidylinositol -4,5-Bisphosphate3-Kinase Catalytic Subunit Alpha), CCNDI(Central Compartment Node Dissection 1). Mutations in two autosomal dominant genes, BRCA1 and BRCA2, account for most of the cases of familial breast cancer. Other gene mutations associated with a high risk of developing breast cancer include TP53 (Tumor Protein 53), PALB2 (Partner And Localizer Of BRCA2), PTEN (Phosphates and tensin homolog), STK11 (Serine/threonine kinase 11) and CDH1(Cadherin-1)as well as other various environmental factors which may cause cancer.[11,12]

Role of the BRCA genes

In the process of replication and DNA (Deoxyribo nucleic acid) repair, two genes BRCA1 and BRCA2 play major roles in transcription and repair of double-strand breaks via homologous recombination.[13] They are inherited in an autosomal dominant fashion with incomplete penetrance. BRCA1(Breast Cancer type 1) and BRCA2(Breast Cancer type2) genes play important roles not only in tumorigenesis but also in cancer progression and outcome. Mutations in either gene allow the affected cells to follow alternative error prone DNA repair pathways of non-homologous end joining (NHEJ) or single stranded (ss) annealing to treat the damaged DNA lesions. The loss-of-function mutations in the genes cause a few of these cells to escape the process of apoptosis thereby accumulating genomic alterations in form of double stranded breaks (DSBs).[13,15]

BRCA1 gene is located on the long arm of chromosome 17 (17-21) encoding a 1863 amino acid long polypeptide. While the Ring domain facilitates interaction of the gene with other proteins, BRCT domain recognizes and binds to specific phosphoproteins to activate transcription.[15] Among the several cellular roles, BRCA1 activates G2/M checkpoint in cell cycle regulation and is also involved in chromatin remodeling.[13,15]

BRCA2 gene is mapped on the long arm of chromosome 13 with 3418 amino acids.[20] It consists of eight copies of BRC repeats and ass DNA binding region. BRCA2 gene is dimeric in structure where two sets of RAD51 are oriented in opposite directions binding to one

surface in the late S and G2 phase while single stranded DNA binds along the long axis at other surface without dissociation.[21] The function of the gene is limited to DNA recombination and repair processes. It regulates the activity of RAD51, which is a highly conserved DNA recombinase, involved in the repair of double-strand breaks and arrested replication forks. At the site of DNA damage, the catalytic RAD51 is recruited by BRCA2. RAD51 interacts with BRC (Breast cancer) repeats and C terminal of BRCA2 gene resulting in its phosphorylation. In addition, RAD51 also links to BRCA1 gene phosphorylating it. The ultimate result is the inhibition or activation of transcription process. Overall, BRCA1 and BRCA2 genes work in sync towards error-free repair of DNA.[13,16]

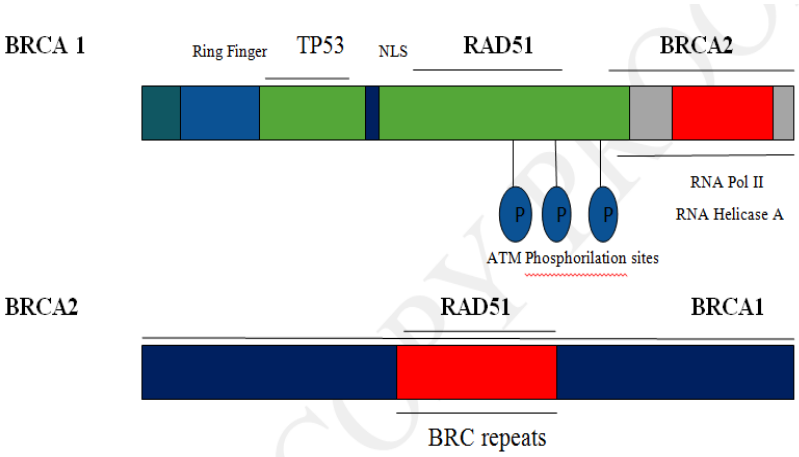

Figure 1: BRCA1 and BRCA2 genes.

Inactivation of the BRCA alleles may result in disruption of the DNA repair mechanism thus leading to detrimental consequences. BRCA disruption causes defects in chromosome structure, cell division, and viability. The aberrations arise in the form of genetic variations or mutations. The so called pathogenic mutations in BRCA alleles may confer a higher risk of developing diseases including different types of cancers. The Breast Cancer Information Core (BIC) database has recorded 1639 and 1853 distinct mutations, polymorphisms and variants in BRCA1 and BRCA2 genes respectively.[17] The most common types of mutations observed are small frameshift insertions or deletions, non-sense mutations or mutations affecting splice sites resulting in deletion of complete/partial exons or insertion of intronic sequences.[16,18]

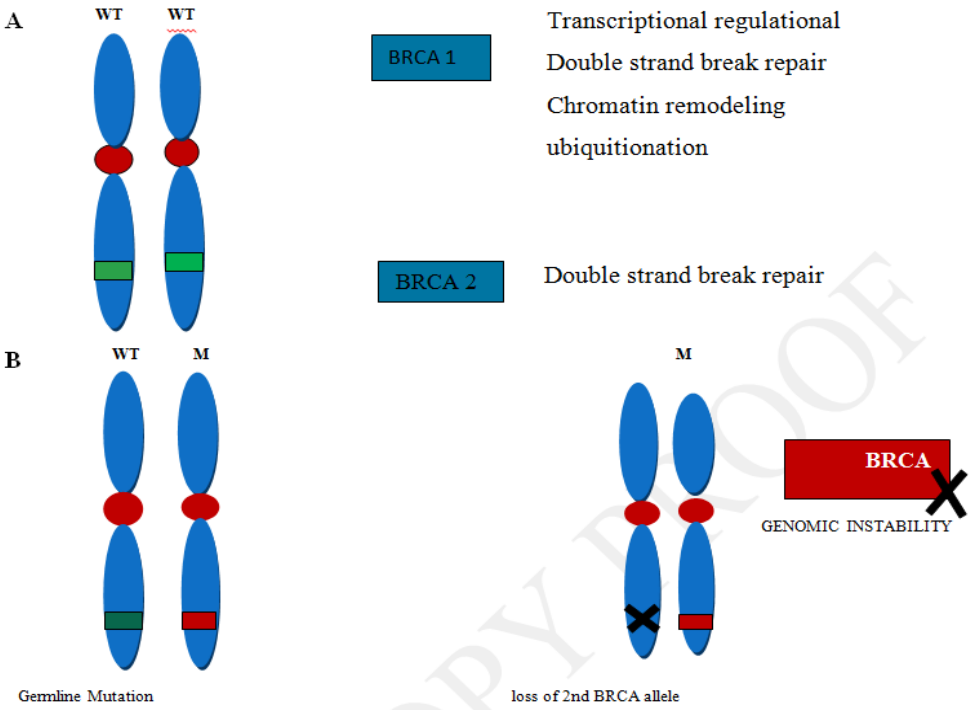

Figure 2: A) BRCA1 and BRCA2 functions. B) Loss of 2nd BRCA allele in BRCA mutation carrier.

Some of estrogen metabolites were shown to cause DNA damage directly (contribute in the breast cancer initiation). Selected causes of estrogen overload (early menarche or late menopause) are at least in part attributed to inherited genetic variations.[19] However, most of determinants of hyperestrogenia are related to the modern, Western lifestyle including low parity, delayed age at first delivery, short duration of breastfeeding, overeating, and limited exercise and so on. Interestingly, the obesity correlates with hyperestrogenia and excessive breast cancer risk only after the menopause.[20] The adverse impact of contraceptive method and internal secretion replacement medical care has been confirmed in some however not all medicine students.[21]

The second cluster of carcinoma predisposing properties deficiency in maintenance of genomic integrity has been recognized solely recently. First all of the known carcinoma susceptibility genes contribute to the sensing or repair of DNA damage; Second, there's a formidable dependableness of phenotyping studies demonstrating relationships between breast cancer risk and constitutional body instability.[22] Unlike lung or bladder cancers, none of environmental carcinogens has been convincingly linked to breast cancer etiology. Contrary to beliefs of many patients, psychological stress is not associated with breast cancer risk.[23]

Factors Associated with Risk of Breast Cancer Development.[16]

Table 1: Risk factors of Breast Cancer.

Risk factors	Incidence
Anthropometric and lifestyle factors	• 20–40% lowers risk of developing overall breast cancer in obese premenopausal women, but increased risk of developing TNBC and ER− tumors. Higher risk of developing breast cancer in obese postmenopausal women. • 70% likelihood of developing ER+ breast cancer in obese postmenopausal women. • ≥15% risk of developing breast cancer in women who gained 20 pounds or more after age 18 years. • 10–20% decrease in the risk of developing breast cancer in women who exercise regularly. • 20% higher risk for women who consumed 2–3 alcoholic drinks per day compared to non-drinkers. • 10% increased risk in women who drank 6–7 alcoholic drinks per week between her first period and the first pregnancy.
Age and race	• 5% of breast tumors are seen in women b40 years of age. In women aged b40 years, non-Hispanic black women have a higher risk of developing breast cancer. • 80% of breast tumors are diagnosed in women aged N50 years. In women N50 years of age, non-Hispanic white women have a higher risk of developing breast cancer. Highest incidence in women N70 years of age. • Black women are diagnosed younger than white women.13% and 11% lifetime risks of developing breast cancer in black and white women, 8–10% lifetime risk of developing breast cancer in Hispanic and American Indian/Alaskan American.
Radiation exposure	• Up to sevenfold increased risk of breast cancer in women treated with radiation therapy to the chest area for Hodgkin lymphoma at a young age.
Hormone replacement Therapy	• Higher incidence of breast cancer in women who use the combination of estrogen and progestin compared to women who used estrogen-only therapy.
Birth control pills	• 20–30% increase in risk of developing breast cancer in women taking birth control pills.
Hereditary	• Twofold increased risk of breast cancer in women with a first-degree female relative with a diagnosis of breast cancer.3–4-fold higher risk if she has more than one first-degree relative with a breast cancer diagnosis.

Diagnosis of the breast cancer

Breast cancer has the greatest mortality rate as compared to the other cancer types. There were 8.2 million deaths in the year 2012 due to cancer, which increased enormously to 8.8 million in the year 2015, as per World Health Organization (WHO) factsheet.[24,25] Since 2005 to 2015, cancer cases increased by 33% worldwide. The count of new cancer cases

worldwide which is expected to increase from 1.5 million per year approximately in 2010 to about 1.9 million per year by 2020 and to 2.1 million per year before the end of 2025.[26]

The Computer Assisted Diagnosis (CAD) system is most widely utilized to assist pathologists to analyze the disease. Mammograms and Computerized Tomography (CT) that uses x-rays of distinct wavelengths, Magnetic Resonance Imaging (MRI).[27]

Mammography

Mammography is the initial step but it hardly detects cancer in dense breasts in adolescent women. Moreover, the mammographic ionizing radiation increases threat to health of radiologists and patients.[27]

Computerized Tomography

CT uses radiations that have a negative effect on organisms, especially for their ability to cause genetic mutations.[28]

Ultrasound screening

Ultrasound screening is recommended for women with dense breast but it has a high false positive rate.[29]

Magnetic Resonance Imaging

In Magnetic Resonance Imaging screening, the patient may feel claustrophobic due to enclosed space inside magnetic tube.[29]

PET/CT and SPECT-CT

Correlated the location of suspicious regional lymph nodes visualized on baseline PET/CT (Photon Emission Tomography/ Computed Tomography)studies with the location of sentinel nodes visualized on SPECT-CT(Single-Photon Emission Computed Tomography) lymphoscintigraphy performed after neo-adjuvant therapy. Recently SPECT/CT combining single photon emission computed tomography lymphoscintigraphic data with CT have gained improved diagnostic accuracy compared to planar lymphoscintigraphy, with better visualization and localization of the sentinel nodes. This technology is routinely used at our center for sentinel node mapping.[30]

Immuno Histo Chemistry

Hematoxylin gets bound to Deoxyribo Nucleic Acid (DNA) and it dyes purple/blue color to the nuclei & Eosin gets bound to proteins and it dyes pink color to other structures. The process to diagnose breast cancer requires an expert and is time consuming.[31]

Computer Assisted Diagnosis of cancer using histopathology (CAD)

The pathologist can be assisted by the CAD system that classifies the image as benign or malignant. This paper focuses on the existing state of art techniques used in CAD system to diagnose breast cancer using histopathological images.[32]

Tumor markers

Tumor markers square measure substances created by the tumors or by alternative cells of the body in response to cancer or sure benign conditions. These markers square measure accustomed value the patient's response to treatment and to notice the presence of metastasis or repeat. The CA 27-29(Cancer antigen 27-29), CA,15-3(Cancer antigen 15-3), CA27.29, carcinoembryonic substance tissue peptide specific substance, p53, cathepsinD, Cyclin E, Nestin and HER-2 square measure tumor markers that square measure usually expressed in individuals with carcinoma. They play a vital role in diagnosing, watching response to medical aid, early detection of metastasis and determination of repeat in patients with carcinoma.[33]

Biopsy procedure

To overcome this, biopsy procedure is carried out to diagnose the abnormality in breast. A biopsy is the physical examination under which a piece of sample tissue is taken out for microscopic examination. The sample is then referred to the laboratory where pathologist examines and analyzes tissues under the microscope. This microscopic examination and study of biological cells, tissues are known as histopathology.[34,28]

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.[3]

Breast cancer therapies

Current treatments for breast cancer include surgery, medicines, and radiation therapy.[35] And the medication of breast cancer mainly includes anti-estrogen drugs[36], Aromatase

inhibitors, Anti-angiogenesis drugs, Monoclonal antibody drugs, Anti-estrogens are very effective on reducing the risk of breast cancer. Aromatase inhibitors also have been shown to be effective in treating women with early stage breast cancer. Anti-angiogenesis drugs can inhibit the development and growth of breast cancer and lead to its ischemic death. Mounting studies showed that the monoclonal antibody drugs had a significant anticancer effect and could improve the survival ability of patients.[37] These agents most of them were expensive and could cause serious side effects after administration. Anthracyclines are better for breast cancer than many other chemotherapy drugs.[38]

Many natural molecules isolated from herbs have significant anti-breast cancer efficacy, such as Paclitaxel, vincristine, cantharidin, sodium injection, Magnolol and etc. Among them, the rapid development of immunotherapy methods is particularly eye catching. Immunotherapy has continued to bring new evangelism to patients in recent years.[38]

Carcinoma in situ or non-invasive breast cancer

If the cancer cells haven't undergone the basement membrane they're in place or non-invasive breast cancers. An invasive cancer is one wherever cancer cells have undergone the basement membrane of the ducts and lobules invasive the encircling adjacent traditional breast tissue and so have the potential to spread. There are two varieties of breast cancer in place.[39]

Lobular carcinoma in situ

Lobular neoplasia represents a spectrum of changes that can occur within breast lobules ranging from atypical lobular hyperplasia to lobular carcinoma in situ (LCIS). It is associated with an increased risk of developing subsequent invasive breast carcinoma. LCIS is usually mammographically occult and is most often diagnosed as an incidental finding in breast biopsies. It was assumed to be premalignant because it was found in association with invasive carcinoma and was therefore believed to be best managed by surgical excision. There is one subtype, pleomorphic LCIS, that may exhibit more aggressive biological behavior than classical type LCIS and this is usually managed as for DCIS by surgical excision.[39]

Ductal carcinoma in situ

Ductal carcinoma in situ of the breast constitutes a heterogeneous group of lesions with variable malignant potential. It is the precursor lesion for most invasive breast cancers, but not all DCIS lesions appear to have the time or genetic potential to progress to invasive cancer. DCIS may occasionally present with symptoms such as bloodstained nipple

discharge. An inevitable consequence of 'over diagnosis' is 'over treatment' which is currently the subject of considerable debate.[40,41]

Herbal medicines

Today public has more interest in herbal remedies than synthetic medicines because herbals contains natural active compound that can support the human health. Globally some common herbs that are used for the treatment of breast cancer like a Green tea, Amla, vitamin D, Black coash, Garlic, Onion, Carotenoids, Ginseng, Turmeric and etc.[42]

Adjuvant therapy

Adjuvant therapy is given after surgery for breast cancer. It may be separated into local treatment (radiotherapy) and systemic treatments (chemotherapy, endocrine and biological therapies). The aim of adjuvant treatment is to reduce the risk of relapse (both local and distant) and to improve disease-free and overall survival. Factors taken into account include tumor size, histology, nodal status and expression of various receptors (estrogen, progesterone and human epidermal growth factor receptor 2 (HER-2). Other factors that must be considered include past medical history, performance status, menopausal status and family history of breast cancer.[43]

Surgical therapy

The surgical treatment of breast cancer is a primary intervention to provide local control, remove any visible or microscopic tumor cells, and obtain final pathologic stage of disease. Several combinations of surgical procedures may be performed, depending on the tumor type, extent, and clinical stage of disease.[44]

Prophylactic Mastectomy

Prophylactic mastectomies are performed to eliminate breast tissue bilaterally, although the removal of all breast cells is virtually impossible. The emerging trend, especially in prophylactic mastectomies is to retain native nipple and areolar tissue with intraoperative sampling of subareolar region to ensure absence of malignant cells. The clinical rationale for keeping native tissue relates to the easy palpation of potential abnormalities in the periareolar region, with visual review of long term imaging of the nipple/areolar complex.[45,46] Rates of contralateral prophylactic mastectomy among this group of women are rapidly increasing.[47] Women must be reminded to continue with long-term follow up despite removal of all visible breast tissue because disease recurrence is possible.[48]

Breast conserving therapy

The advent of breast-sparing surgery in the form of lumpectomy was a landmark change30 years ago in the locoregional control of noninvasive and invasive breast cancer. Lumpectomy with SLNB or axillary dissection results in the same mortality rate as modified radical mastectomy. Radiation therapy follows the lumpectomy to treat part or the whole breast as prevention for ipsilateral recurrence.[49] In breast-conserving surgery; palpable breast tumors are removed under conscious sedation or general anesthesia via a small incision, typically 5 to 7 cm in length.[3] Needle localization is necessary to pinpoint the area to be removed in nonpalpable lesions.[50] To provide support of the surgical breast, prevent hematoma formation, and improve pain control. Breast conserving surgery is contraindicated in women with a history of previous chest or breast radiation, current pregnancy, diffuse suspicious appearing micro calcifications, wide spread disease, or positive margins that were not cleared with repeat lumpectomy.[51,52]

Lumpectomy

A lumpectomy is successful when the entire lesion is excised and the pathology report indicates negative margins.[53] The goal of negative margins is to use accurate localization and excision with appropriate margins to decrease the risk of local recurrence of tumor while minimizing loss of volume and maximizing aesthetics.[51,52] The exact number of millimeters required to define a clear margin (1 to 10 mm) remains controversial, although tumor at the inked margin can occur in up to 40% of cases, which is unacceptable because of a 2-fold increase in ipsilateral recurrence.[53] Pathology results that indicate one or more positive margins require additional surgery to ensure complete removal of all cancer cells[54]. A re excision of margins (e.g., relumpectomy) may be attempted for one or two positive margins, although mastectomy is indicated in the case of multiple positive margins. Attempts to improve positive margins, including the use of intraoperative real time ultrasound, multiple frozen sections, or non surgical ablation [55,56]

Mastectomy

A mastectomy requires general anesthesia and involves an oblique lateral incision from the mid sternal edge to proximal tail of Spence Breast tissue is dissected vertically from the clavicle to infra mammary fold, and horizontally from sternum to midline axillary line and the edges are approximated with subcutaneous absorbable sutures.[48] Skin sparing mastectomy is common, especially if immediate or delayed reconstructive surgery is

planned.[57] Healing requires1-4 weeks for the chest wall, and several weeks to months to regain full range of motion in arm and chest wall. A simple or total mastectomy is used to manage multi-centric DCIS, whereas a modified radical mastectomy is indicated for large tumors. The modified mastectomy includes removal of the entire breast and level one and two axillary lymph nodes.[3,57]

Surgical management of the axilla

Identification of positive lymph nodes in the ipsilateral axilla is one of the most important predictive prognostic indicators. Therefore, with the exceptions of contralateral or bilateral prophylactic mastectomy, all women should undergo SLNB or axillary dissection on the affected side to examine axillary contents and identify pathological stage of disease.[58]

Sentinel lymph node biopsy

SLNB requires an experienced sentinel lymph node team because proficiency is measure by the frequency of successful procedures compare with postoperative pathology results. SLNB can be performed the day of breast surgery with peritumoral injection of 99mTc sulphur colloid at least 1 hour before surgery, followed by a subareolar lymphatic plexus injection of vital blue dye in the operating room and five minutes of gentle whole breast massage. The axillais surveyed with a gamma probe to find the most intense area of radioisotope uptake. Once identified, a small incision is made in the axilla to allow the surgeon to identify the visible network of blue dye that corresponds with an increased auditory sound from the gamma machine.[58,59,60]

Drain placement may occur if a significant number of nodes are removed, or if the SLNB is indecisive and axillary dissection is performed. Discussion should also occur that the final pathology report defines the final pathological stage of disease.[61]

Axillary node dissection

Axillary node dissection is the dissection of levels I and II lymph nodes with sparing of the axillary vein main trunk, long thoracic nerve, and thoracodorsal neurovascular bundle, which is performed under general anesthesia.[62] The effect of axillary node dissection on treatment decisions is important because systemic treatment is based on presence or absence of nodal disease, although no longer the number of positive lymph nodes. The value of axillary node dissection in locoregional control exists in the prevention of disease recurrence.[63]

SLNB significantly lowers the rate of axillary complications such as seroma, infection, pain, and edema as compared with axillary node dissection.[64]

Radiation therapy

Radiation therapy is an essential component of local treatment of the breast, most commonly to treat the breast after a lumpectomy or following mastectomy caused by tumor burden secondary to a large tumor or multiple positive lymph nodes. Radiation begins 4 to 6 weeks after surgery or following chemotherapy. The omission of radiation therapy following lumpectomy increases the risk of ipsilateral breast recurrence, and may negatively affect the risk of distant recurrence.[65,66]

Whole breast radiation

Whole breast fractionated radiation therapy is administered to the entire affected breast over 5 to 7 weeks, including a boost of several additional treatments directed at the tumor.[73] Whole breast radiation therapy following a lumpectomy has demonstrated equal mortality rates as mastectomy with fewer long-term side effects.[66,67] A radiation boost may decrease local recurrence, which may add to the absolute gain in younger patients because of their anticipated longer life span.[67] Women who require daily radiation therapy may have conflicts related to transportation, time, work, children, finances, mobility, or access to care issues, and may eliminate this important component of local therapy.[65]

Accelerated partial breast radiation

The most common type of APBI is 3-dimensional conformal breast therapy. Using special measurement techniques and the linear accelerator, 3- dimensional conformal breast therapy is administered in 10 twice-daily treatments with a boost to lumpectomy site. In addition to the various types of APBI, prone radiation therapy in the smaller breast or deep malignancy is gaining popularity as a means to lessen radiation exposure to the hear.[63]

Endocrine Therapy

A important key role for endocrine medical care in treatment of carcinoma. Endocrine medical care remains vital in biological time ladies with internal secretion receptor positive carcinoma. Internal secretion medical care may be a cancer treatment that removes hormones or blocks their action and stops cancer cells from growing. Hormones area unit substances created by glands within the body and circulated within the blood. Some hormones will cause sure cancer cells to grow. If tests show that the will cancer cells have

places wherever hormones can attach (receptors), drugs, surgery, or irradiation is employed to cut back the assembly of hormones or block them from operating.[3,67]

Drugs including in endocrine therapy Tomaxifen, Rolaxifen, toremifene, Anatrozole, Exemestane, Letrozole, Fulvestrant, Estradiol, Fluoxymesterone.[67]

Precision medicine for breast cancer

Precision medicine is associate degree approach to patient care that permits doctors to pick treatments that area unit presumably to assist patients supported a genetic understanding of their sickness. This may even be called personalized medication.[3,31,68]

Chemotherapy for breast cancer

Chemotherapy (also known as chemo) may be a variety of cancer treatment that uses medicine to kill cancer cells.[3] For women with estrogen receptor positive(ER+) metastatic breast cancer (MBC), the options are either endocrine therapy (ET) or chemotherapy. ET is often used as first line treatment for metastatic disease in those who have soft tissue, bone predominant, or low volume visceral disease, reserving chemotherapy for those with more aggressive disease or visceral crisis.[68] Chemotherapy is used as initial therapy, further treatment depends on whether chemotherapy is used for a fixed number of cycles toxicity has halted chemotherapy or whether chemotherapy is used until disease progression. In the first two scenarios, there is the option of introducing ET after chemotherapy, and as well as the other options of maintenance chemotherapy and concurrent chemo-ET.[69]

Epirubicin, Docetaxel, Gemcitabine, Doxorubicin, Cyclophosphamide/Methotrexate/5 Fluorouracil, Trastuzumab, Paclitaxel, Exemestane.[67,69,70]

Immunotherapy

The success of immune checkpoint inhibitor therapy in immunogenic cancers such as breast has underscored the importance of the adaptive immune system in cancer eradication. The adaptive immune system is composed of lymphocytes, both T-cells and B-cells, and is defined by the ability of those cells to specifically respond to immunogenic, i.e. antigenic, proteins expressed on and in cancer. Immune checkpoint inhibitor agents allow tumor educated T-cells to recognize cancer, proliferate, and limit tumor growth. The adaptive immune response is also associated with the development of immunologic memory, the

ability of lymphocytes to respond again at a distant time point if ever exposed to tumor cells. Moreover, T-cells capable of killing tumors cells are of a Type I phenotype; CD4 T-cells in the tumor microenvironment secrete Type I cytokines such as interferon-gamma (IFN-g) and tumor necrosis factor-alpha which activate antigen presenting cells and support the development of cytotoxic CD8 T-cells needed to induce cancer death.[71]

Targeted therapy

Molecular targeted therapy has been considered a milestone in precision medicine for breast cancer. A different subtypes and sensitivity to various drugs, such as hormone receptor, HER2, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), mechanistic target of rapamycin (mTOR), and cyclindependent kinase 4/6 (CDK4/6). Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown promising activity in breast cancer associated with breast cancer 1 (BRCA), the expression of which is commonly observed in TNBC. HER2 inhibitors [such as trastuzumab, pertuzumab, lapatinib, and trastuzumabemtansine] (PI3K)/v-akt murine thymoma viral oncogene homolog (AKT)/mTOR inhibitors (everolimus, buparlisib, and ipatasertib), PARP inhibitors (such as veliparib, talazoparib, olaparib, and iniparib), CDK 4/6 inhibitors (such as palbociclib, abemaciclib, and ribociclib), VEGF inhibitors (bevacizumab), and immune checkpoint inhibitors (pembrolizumab and avelumab).[72]

Stem cell transplants therapy

Stem cell transplants help restore blood-forming stem cells in people who have had their destroyed by certain cancer treatments.[3] Fractional irradiation caused lower level of reactive oxygen species (ROS) in breast cancer stem cells (BCSCs) compared to highly differentiated tumor cells, suggestive of a radio resistant phenotype .CSCs are the root of cancer development and characterized by the common features of mammary stem cell, including quiescence, self-renewal, and differentiation potential. The self-renewal ability gives BCSC a survival advantage by efficiently repairing the DNA damage, while the differentiation potential confers BCSC a tumorigenic ability. The action closely links the changeable stem like properties to the diverse tumor microenvironments via intracellular signaling. The over activation of anti-apoptotic PI3K signaling pathway and antioxidant nuclear factor E2-related factor 2 (NRF2) signaling pathway also confers BCSCs a more resistant phenotype than non-CSCs against cytotoxic drugs or irradiation beam induced ROS attack and apoptosis.[73]

FDA Approved Drugs for breast cancer in 2019

Herceptin Hylecta (Trastuzumab)

Company :Halozyme

Approval Status : Approved February 2019

Specific Treatments : HER2-overexpressing breast cancer

Mechanism of Action

Herceptin Hylecta could be a mounted dose combination of trastuzumab, a HER2/neureceptor antagonist, with Halozyme's proprietary recombinant human spreading factor accelerator. The HER2 or cistron encodes a transmembrane receptor macromolecule of 185 kDa, that is structurally associated with the epidermic protein receptor. Hyaluronan could be a saccharide found within the animate thing matrix of the connective tissue tissue. And contains a half-life of roughly 0.5 days. Spreading factor will increase porosity of the connective tissue tissue by depolymerizing hyaluronan. Within the doses administered, spreading factor in Herceptin Hylecta acts transiently and domestically. The results of spreading factor area unit reversible and porosity of the connective tissue tissue is rehabilitated inside twenty four to forty eight hours.[74]

PIQRAY (ALPELISIB)

Company : Novartis

Approval Status : Approved May 2019

Specific Treatments: HR+, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer

Mechanism of Action

Piqray (alpelisib) is an inhibitor of PI3K with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in-vitro and in-vivo models. In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer. PI3K inhibition by alpelisib treatment has been shown to induce an increase in estrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and

fulvestrant demonstrated increased antitumor activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.[75]

CONCLUSION

This overview of the literature shows that breast cancer has several different stages which determine the aggressive biology of this disease and Locoregional therapies like surgery and radiation therapy have shown to improve local recurrence, Since the consistent use of neoadjuvant chemotherapy, overall survival increased. And however, new and additional agents are necessary to improve the standard treatment since it remains a disease with a dismal prognosis.

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