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Breast Cancer: Diagnosis and Treatment

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ABSTRACT

Cancer cell are undisciplined normal cells that grows disorganized way leads to life threaten and serious complication. Cancer cell can invade any organ and cause disruption in the functioning of the tissues. Breast are the mammary glands aids in production of milk in postnatal mothers, apart from the vital function breast are glands develop after puberty, the parenchyma cells of breast are risk of developing abnormal growth leads to condition called Breast cancer. According to research 23% female and 0.5 to 1% of males are facing the problem of breast cancer. Breast cancer is second leading cause of death in men and women, globally 66% of deaths are due to breast cancer. Death due to breast cancer can be delayed by proper diagnostic techniques, these techniques not only delay the death and also increases the survival rate of the population. Early detection of the breast cancer gives better care, prevent complication and effective management. A number of research study identified the diagnostic tools and therapy for breast cancer; however, these tool and treatment are identified in late stage, and significant detection of breast cancer is still lagging. Hence, the present review article is an effort to comprehensively describe the early and advanced diagnostic tools for detection of breast cancer and advanced therapeutic management for breast cancer.

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Introduction

Cell is the basic structural and functional unit of an organism; cell replicates divide to multiple to achieve more functions and structure. Cell division is natural, dynamic and continues process of any living organism. However, the division of cell when affected by carcinogens the nature and quality of cell division is disorganized, lead to a condition called cancer. Cancer is abnormal proliferation of the immature cells and uncontrolled growth of cells. Various structures can be affected with cancer they are lungs. Kidneys, bones, brain, breast.

Carcinoma of breast originates in breast tissues, occurs due to breast cells mutate and grow out of control, forms a mass tissue called tumor. Breast cancer can occur in lobules, ducts and connective tissue; majority began in ducts and lobules. Uncontrolled and managed breast cancer can spread to other structured of the body like lungs, bones, uterus via blood and lymph vessels termed as metastasis. Both the genders: Men and women can develop breast cancer; the risk factors include age more than 50 years, inherited genetic change mutation, unhealthy reproductive history, dense breast, family history of ovarian and breast cancer, exposure to radiation, obese, hormonal treatment, alcohol consumption, smoking habits. Identification of the breast cancer in early stage is still lags, several techniques are available to detect and specifically diagnose the breast cancer.

One in eight women develops breast cancer, according to The International Agency for Research on Cancer reported that 66% increase in global number of cancer deaths. The diagnosis of breast cancer traditionally includes mammography, ultrasound, and bioimaging. These techniques detect breast cancer at late stages, early detection and advanced diagnostic tools are in real need to develop effective therapeutic regimen [1].

Diagnosis of Breast Cancer

Breast Cancer is Heterogeneous

the histological and molecular presentations are different. Conventionally, the management of breast cancer was based on tumors' clinical presentation, biomarkers released and histopathological demonstration [2].

The World Health Organization, 2012 classified breast cancer as Carcinomas and Sarcomas, Carcinomas breast cancer originates from epithelial cell of lobules and terminal ducts and Sarcomas breast cancer originates from connective tissues, blood vessels and myofibroblast. The lesions in carcinomas or sarcomas exhibit elevation in estrogen and progesterone, the histological understanding of breast cancer helps in managing chemotherapeutic and endocrine therapy [3,4].

The three-tier grading system of TNM provides the order breast cancer heterogeneity, the TNM grading analyses the percentage of (tumor in glands and tubular structure T, degree of nodes N and mitotic rate M) simplifies the breast cancer staging and spread [3].

The molecular biomarker gives desirable explanation for breast cancer heterogeneity, the biomarkers are estrogen receptors, progesterone receptors and human epidermal growth factor receptors. They are further subtype categories as Luminal A & B, HER2 enriched, triple negatice or basal like & normal like

breast cancer. The classification helps in prognosis, treatment. The lack of estrogen repeptors, progesterone receptors and human epidermal growth receptors2 leads to higher staged nuclear grade cancer with intense mitotic action and poor prognosis the Triple Negative Breast cancer are tolerant of endocrine therapy due to no hormonal expression [5-9].

Androgen receptor is another prevalent sex steroid harmone is used in subtyping breast cancer, in estrogen receptor breast cancer, androgen promotes cell proliferation and spread by acting at different androgen receptor signaling pathways [10].

The expression level of the cell proliferation gene and harmone receptors determines the systemic management currently four biomarkers are identified Cancer Antigens 15-3, Cancer Antigens 27-29, Human epidermal growth factor receptor2 and circulating tumor cells in body fluids. The American society of clinical oncology recommends the gene expression analysis of Cancer Antigens 15-3 and Cancer Antigens 27-29 together with bioimaging for constant monitoring of treatment persistence. The circulating tumor cells measures and monitors the metastasis of breast cancer [11].

Breast Cancer gene 1 & 2 (BRCA1 & BRCA2) are most common genes implicated in Breast cancer risk assessment [12].

Tumor protein 53, is a rich suppressor protein and most mutated gene that encodes more than 12 isotopes of tumor protein. The triple negative breast cancer contains mutated p53 gene. The mutant specific antibodies have great clinical diagnostic potential in targeting minute alterations embedded in various disease states [13].

Ataxia Telangiectasia Mutation is tumor suppressor gene like Tumor protein 53 involves Deoxyribonucleic acid (DNA) repair mechanism. Mutation in ataxia telangiectasia exhibits greater risk of breast cancer. The Ataxia Telangiectasia is associated with autosomal recessive disease, patients homozygous for it will be primarily affected and the heterozygous patients developing breast cancer is 2 to 4 times higher than the general population. The Ataxia Telangiectasia syndrome patients are relatively at of developing breast cancer 6.02% by 50 years of age and 32.83% by 80 years of age [14].

Phosphatase and Tensin Homolog (PTEN) is majorly associated with cellular function such as genomic stability, cell proliferation and motility through PI3K pathway. Phisphatase and Tensin Homolog gene mutation is implicated in wide variety of sporadic cancers [15].

Seven in Absentia Homolog (SIAH) is a conserved gene, mutation of SIAH rarely accounts for specific disease, SIAH1 gene mutation is associated with breast cancer. The results of specific gene causing breast cancer are hard to interpret as the interference of other tumor suppressor gene located on same chromosome [16].

Insulinoma Associated Protein1(INSM1) was identified as fetal pancreas and nervous system as a zinc finger transcription factor, recently observed in high grade and aggressive breast carcinomas, luminal-B subtype. The INSM1 expression as a favorable prognostic biomarker, and useful in stratifying Neuroendocrine tumors [17].

Matrix Metalloproteinase 9 (MMP9) are endopeptidases acting on a broad range of proteins like gelatin, collagen and elastin. MMP9 is a potential biomarker in breast cancer, it disrupts membrane trigger angiogenic switch which initiates carcinoma invasion, MMP9 also activates cytokines, invades microenvironment of distant organs enhancing metastasis [18].

Saliva Biomarker recently received much attention as noninvasive biomarker for early breast cancer detection. The Zhang study initiated de novo biomarker, established total nine biomarkers eight messenger RNA (mRNA) and one Cancer Antigen Protein6 (CA-6) with clinical diagnostic accuracy of 92%. Further salivary autoantibodies also identified to play vital role in screening breast cancer [19].

Tumor Associated Autoantibodies (TAABs) are antibodies produced by patients' immune cells against tumor associated antigens. These antibodies are 'tumor signals' act as biomarkers for cancer identification, with advanced technological test, serological analysis, recombinant DNA cloning technology early detection of antigens can be done [20].

Diagnosis of Breast Cancer

Mammography a gold standard technique in screening of breast cancer, a low dose x-ray examines each breast, lumps, nipples, skin changes. The mammogram a digital image of breast are taken horizontal and vertical to encircle and examine entire breast, mammogram can interpret lesions, mass, calcifications, architectural distortions in breast tissues.21 Mammogram fails to identify fibro glandular breast tissue which masks underlying breast cancer. Mammogram despite golden standard is with limitation, the limitations are substituted by magnetic resonance image, digital breast tomosynthesis, ultrasound and biopsy [22].

Molecular imaging, magnetic resonance imaging is standard technique uses magnetic field, analyses lumps that may need biopsy, a contrast reagent is injected into blood steam enhancing pinpoint image analysis of breast. The spread of breast cancer can be analyzed by radioactive chemicals, Scintimammography, positron emission mammography screening techniques. The advanced technology Magnetic resonance imaging like dynamic contrast enhaced MRI (DCE-MRI), chemical exchange saturation transfer MRI (CEST-MRI) helps in evaluating metabolic heterogeneity with tumor. These techniques have a risk of radioactive material exposure, hence limited to highrisk women patients' [21].

Ultrasound, a complementary procedure confirms positive mammagram. Automated Breast UltraSonography (ABUS) is used for dense breast tissue exams. Contrast enhanced ultrasonography (CEUS) and microvascular imaging determines the malignant and benign tumors and analyses the blood flow to the local tissues, and also predicts the efficacy of neoadjuvant chemotherapy on breast cancer [23].

Digital imaging, currently newer techniques have emerged promoting early diagnosis and screening of breast cancer, the Digital Infra red Thermal Imaging (DITI), Digital Image based Elasto Tomography (DIET) and Electrical Impedance Scanning or Spectroscopy (EIS).

DITI measures the skin temperature difference to reflect the physiological changes such as vasodilatation, neovascularization, inflammation, lymphdysfunction, congestion around breast borders. The changes are recorded in thermogram to study the breast cancer [24].

DIET technique uses the vibrational energy in graphing the location of tumor. A surface motion low frequency (5 to 100Hz) sinusoidal waves are induced to breast, and th oscillations are recorded by digital camera tracking fiducial markers. Areas with different, vibrations response compare to control tissue are considered potential tumors, feeding theses responses on algorithm shows the delay in surface vibrations detecting tumor angular location, depth, and size [25].

Electrical Impedance Scanning (EIS) works on principle that tissues have different electrical property under different metabolic conditions. Cancer tissues create a finite metabolic change in tissues. EIS can discriminate diseased tissue from normal tissue measures accurate cell shape, structure, depth, intracellular and extracellular environment and lipid membrane compositions [26].

Biosensors are noninvasive, inexpensive analyzer provides a quick response without compromising its specificity and selectivity, biosensors are capable of detecting abnormalities that results due to disease [27].

Biochemical recognition elements (BRE) are multiple bioreceptors employed to detect biomolecules (antibodies, aptamers, enzymes, Circulating Tumor cells) in a sample detected by biosensors. Antibodies are most common BREs used in biosensors contribute real nano sense at detecting breast cancer. A newer generation sensitivity are designed to overcome limitation of monoclonal and polyclonal antigen binding domains, these biomarkers directly detect breast cancer by using enzymatic probes, flurescence probes, or cross linkers. Currently researchers designed a string of specific nucleotide or peptide sequences, function on same principle as antibodies, as tight target binder known as aptamers. Nucleic acid aptamers and peptide aptamers (NAAs) can bind to high affinity specific biomolecules helps in determining the breast cancer biomarkers [37].

Apart from aptamers and antibodies, cDNA-based hybridization biosensor used to investigate breast cancer detection. Using modified cDNA hybridization techniques microRNAs and BRCA1 gene are detected. Biochemical recognition elements and biotransducer used as biosensor. The optical transducer, electrochemical, piezoelectric biotransducers,thermometric and magnetic based transducers targeted BRCA1in early detection. Surface Plasmon resonance (SPR) biotransducer is realtime sensing and analyzing changes in refractive index upon interreaction with labeled biomolecules determine the sensitivity of detecting the biomarkers like Cancer Antigen15-3 [28].

Recently the research in **Quantum Dots (QDs)** and nano crystals gained momemtum in early identification of breast cancer and Quantum Dots as nano lables structures the platform for antibody, protein, aptamer. Unlike enzyme based label systems, the QDs lable electrochemical sensing eliminates the substrate requirement, surpasses enzymes, thermal instability and provide quick analysis. Biosensor offers quick, simple and inexpensive diagnostic tool to detect breast cancer.

Advanced Breast Cancer Detection Systems

Multiple Gene Prognostic Assays, several genetic aberrations in women have a predisposition to breast cancer. Currently there are seven prognostic multigene signature analyzing tests for breast cancer [29].

Breast cancer Index test (BCI), is a multigene assay used as adjunct tool to operate practice. The BCI developed by Biotheranostic Inc, records a set of five proliferative gene expression, termed as Molecular grade Index (MGI) and gene ratio of HOXB13: IL17BR (H:I) predicts the breast cancer outcomes [30].

The MammaPrint Test, is a genomic test developed by Agendia for early stage breast cancer diagnosis. It is a prognostic test stratifies early staged hormonal Breast cancer. MammaPrint Test is used as guide on therapy need for high risk with node negative breast carcinoma [31].

The Mammostrat Test, is a protein based IHC assay. The protein are TP53, NDRG1, CEACAM5, HTF9C and SLC7A5 have implicated in breast cancer recurrence. Mammostrat test evaluates early staged breast cancer, analyzing and informing for adjuvant therapy [31].

IHC4 Test, is hormonal receptors protein based assay, four primary proteins, estrogen receptor, progesterone receptor, Human epithelial receptor2 and Ki67 expression, were used as biomarkers to define the molecular subtype [32].

EndoPredict Test, (EP) is a twele multigene signature assay, examines biopsied tumor tissue for eight cancer realated gene, three RNA reference gene and one DNA reference gene developed by Myriad Genetics. The test score reflects tumor size and nodal status stratifies breast cancer as low or high risk for distant metastasis [33].

Prosigna/Prediction Analysis of Microarry50 Test, (PAM50) is RNA based gene molecular signature assay developed by NanoString Technologies, helps in profiling patients' tumor and understand its behavior. It analyzes the relapse/ recurrence based on breast cancer intrinsic hormonal subtyping. In PAM50 signature assay a fluorescent probes used, mRNA amplification, the results are digitalized fed into algorithm that translates the tumor behavior or biology into actionable clinical results [34].

Oncotype Dx Test, is most valid multigene signature assay, analyzes the RNA expression of 21 gene implicated in cancer proliferation and treatment response. The Oncotype Dx Recurrence Score (RS) stratifies early stage breast cancer into low, intermediate and high risk recurrence [35].

Treatment of Breast Cancer

The treatment of the breast cancer, is a multiple approach, the standard of care is the best treatment available for managing early stage and local advanced breast cancer. A multidisciplinary health team includes physician, nurses, pharmacist, counselor and nutritionist [36].

Medication Approach

Chemotherapy, is the use of drug to control growing, dividing and multiplying the cancer cells. The drugs given before surgery to shrink the tumor and reduce risk of recurrence, before surgery if chemotherapy called Neoadjuvant chemotherapy, if after surgery if chemotherapy called adjuvant chemotherapy.

Some chemotherapy drugs are Docetaxel, Paclitaxel, Doxorubicin, Epirubicin, Fluorouracil, Methotrexate.

Harmone therapy, is endocrine therapy effective in estrogen and progesterone receptors positive tumors, these tumors use harmones to boost their abnormal growth, blocking the harmone prevent cancer recurrence.

The harmone therapy for breast cancer is different than Menopause harmone therapy. The therapy begins 3 to 6 months before surgery and continued after surgery.36

Types of harmone therapy after menopause and before menopause used are Tamoxifen (blocks estrogen from binding to breast cells), Aromatase inhibitors (decreases the amount of estrogen made in tissues by blocking aromatase enzyme and suppressing ovaries from making estrogen), ovarian ablation is surgical removal of ovaries to stop estrogen production.

Targeted therapy, is the treatment of specific genes, proteins or tissues environment that contribute to cancer growth and survival. In Human Epidermal growth factor Receptors (HER2) positive breast cancer the targeted therapy drug used are Trastuzumab, Pertuzumab, Neratinib for 1 to 3 weeks through intravenous infusion for various stages of breast cancer.

Bone modifying drugs, helps in blocking bone destruction, strengthens the bone. The drugs are Bisphosphonates and Denosumab [36].

The breast cancer with BRCA1 and BRCA2 gene mutation, non metastatic are managed by Olaparib (PARP inhibitor, destroy cancer cells by preventing them from fixing damage to the cells), Abemaciclib (CDK4/6 inhibitor, targets protein in breast cancer called cdk4/6 stimulates cancer cell growth).

Immunotherapy, improves the immune system and kills the cancer cells, used for high risk, early stage and triple negative breast cancer. The drug used with combination with chemotherapy Pembrolizumab.

Neoadjuvant systemic therapy, is treatment given before surgery to shrink a large tumor or reduce risk of recurrence. The chemotherapy, immunotherapy, hormonal therapy, and targeted therapy uses neoadjuvant therapy.

Surgical approach

Surgery is the removal of tumor and surrounding healthy tissue during an operation. Surgical approach along with medication, chemotherapy, harmone therapy are used to curative management. The various surgeries for breast cancer are.

Lumpectomy, is removal of the tumor and small cancer free margin of healthy tissues around tumor. Is also termed as breast conserving surgery, partial mastectomy, quadeantectomy, segmental mastectomy.

Mastectomy, is surgical removal of whole breast, by preserving skin called skin sparing mastectomy, nipple are preserved called nipple sparing mastectomy.
Lymph node removal, cancer cells are found in axillary lymph nodes.

Sentinel lymph node and Axillary lymph node dissection is surgical removal of two or more lymph nodes under arms receives lymph drainage from the breast. The procedure helps by avoiding the removal of larger number of lymph nodes and reduces risk of lymphedema.

Reconstruction Surgical Approach

After mastectomy or lumpectomy, breast are recreated from other parts of the body called as Tissue flap procedure – Transverse rectus abdominis muscle flap (muscle of lower stomach wall) Latissimus dorsi flap (muscle of upper back), Deep inferior epigastric artery perforator flap (tissue from abdomen), Gluteal free flap (muscle of buttocks and upper thigh) or synthetic implants (Prosthetics) called reconstructive surgery, breast reconstruction is perfomed immediately after mastectomy called as immediate reconstruction and surgery done after some time in future called delayed reconstruction.

Radiation therapy

Radiation oncologist uses high energy x-rays and other radioactive waves are used to destroy cancer cells. Various types are.

External beam radiation therapy, in which the whole breast is exposed to radioactive treatment that can last for several days.

Intra operative radiation therapy, in this the radiations are given using probe in operation room.

Brachytherapy, the radioactive seeds are placed inside into the tumor.

Partial breast irradiation (PBI), is focused radiation therapy given directly to the tumor area instead of entire breast, more common after lumpectomy. PBI targets the radiation to tumor cells results in shortens the amount of time need to receive radiation therapy.

Intensity modulated radiation therapy (IMRT), is advanced method in which external beam radiation therapy to breast, the intensity of radiation directed to breast are varied to better target. IMRT lessen the radiation dose, reduces risk of damaging heart, lungs and skin.

Proton therapy, is use of a high-energy proton's beams kill the tumor cells, reduced the radiation reaching heart.

Adjuvant radiation therapy, in which the radiations given after the surgical intervention.

Neoadjuvant radiation therapy, in which radiations given before the surgical approach to shrink the large tumor and make the tumor easy to remove.

Complementary therapy, it is integrative treatment concentrate on older age patients, physical, emotional, and social concern. Integrative medicine uses medicine with complementary therapies such as mind-body practice, natural products, lifestyle changes these includes Music therapy, meditation, stress management, yoga, massage, acupressure and acupuncture [36].

Conclusion

Breast cancer arises initially in ducts and lobules called in suit causes no symptoms and minimal potential for spread, overtime these in suit cancer may progress to breast cells, spread to lymph nodes cause regional metastasis, to other organs distant metastasis. Breast cancer when widespread can lead women to death, globally 685000 died due to breast cancer, the mortality of breast cancer has come down in last decade and improvement in the survival due to early detection and management. Woman having human papillomavirus infection, cervical cancer, age, obesity, family history of breast cancer, history of radiation exposure, reproductive history, postmenopausal hormonal therapy, the BRCA1, BRCA2 and PALB-2 gene mutation greatly increases breast cancer risk, develops symptoms of lump, alteration in size, shape, appearance, change in nipple with discharge, advanced cancers can erode

through skin opens as ulcer, these impairment in breast tissues are studied by biomarkers, molecular studies, imaging, receptors studies, genetic assay studies, hormonal studies identify the stage of breast cancer aiding in treatment by surgical, chemo, radio, adjuvant, neoadjuvant, hormonal, behavioural management. The health promotion for early detection, timely diagnosis and comprehensive breast cancer management are pillar to achieve better treatment, the knowledge of advanced current diagnostic and management modalities available for the treatment of breast cancer helps in reduction of suffering of the women diagnosed with the breast cancer.

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