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“An Update on the Screening, Diagnosis & Management of Breast Cancer - A Review with Considerations for Future Fertility”

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Abstract

The diagnosis along with management of Breast Cancer (BC) are going through a prototype switch from the one size fitting all towards the period of individualized medicine. With the advances in diagnosis that is inclusive of sophisticated methods like molecular imaging in addition to genomic expression profile aid in enhancement of tumor characteristics to get unraveled. With these diagnostics, in combination with the newer surgical strategies in addition to radiation therapy cause a strategy that is inclusive of multiple disciplines cooperating with each other for reduction of recurrence to the utmost minimum. Here we conducted a review utilizing search engine PubMed, google scholar; Web of science; Embase; Cochrane review library utilizing the MeSH terms like surgery; presence or absence of Estrogen Receptor (ER); Progesterone Receptor (PR); Human Epidermal growth factor Receptor (HER2); chemotherapy; Triple Negative Breast Cancer (TNBC); Endocrine therapy; metastases; Radiotherapy; Imaging modalities; causes of TNBC; drug resistance; prognosis; markers for TNBC; effective tamoxifen; negative neo adjuvant chemotherapy; gene markers; role of microRNAs, from 1980's till august 2021. We found a total of 442800 articles out of which we selected 86 articles for this chapter on update on breast cancer management. No meta-analysis was done. Further, we have tried to explore a lot of modes by which TNBC treatment success can get escalated inclusive of the newer utilization of H2S pathway in cancer as well as mode by which it might work. Further, with the escalated 5 yr survival along with advances in ovarian tissue cryopreservation oocyte cryopreservation prior to chemotherapy as well as radiotherapy one can consider ovarian tissue transplantation in such cases. With BCS an attempt at cosmetic surgery aids in women leading a more normal life. Thus, we have tried to comprehensively detail all these features.

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Introduction

A Breast Cancer (BC) represents a malignant tumor, which takes place in the mammary epithelium. Recent epidemiology displays a growing incidence of BC on a yearly basis, with a trend of involving younger women [1,2]. The number of new cases have reached 16.71 million /yr, being the 1st in cancer incidence in women [3,4]. In the last 2 decades ,absolute number of BC cases has increased worldwide by 1.4 times ,with incidence in most countries and regions having increased by 30-40% [3,4].In 2014, it was demonstrated that Chinese women with BC had 12.2% and 9.6% of the total new BC cases with the associated deaths respectively [5]. The rise in incidence of BC worldwide has raised the burden regarding medical resources. Hence, it is essential to conduct continuous, effective prevention and control methods on a global scale for decreasing the incidence and deaths, associated with BC. At present, we have tried to detail the strategies utilized for diagnosis in addition to management of Breast cancer. These strategies are inclusive of advocated screening, diagnostic imaging modalities along with pathological evaluation to estimate the total amount of disease, role of surgery and radiation therapy, besides various systemic alternatives like chemotherapy, endocrine therapy, in addition to targeted agents (figure1) [rev in ref 6]. Further the how potentially functional imaging aids in this newer period of utilization of individualized, tumor-particular therapy.

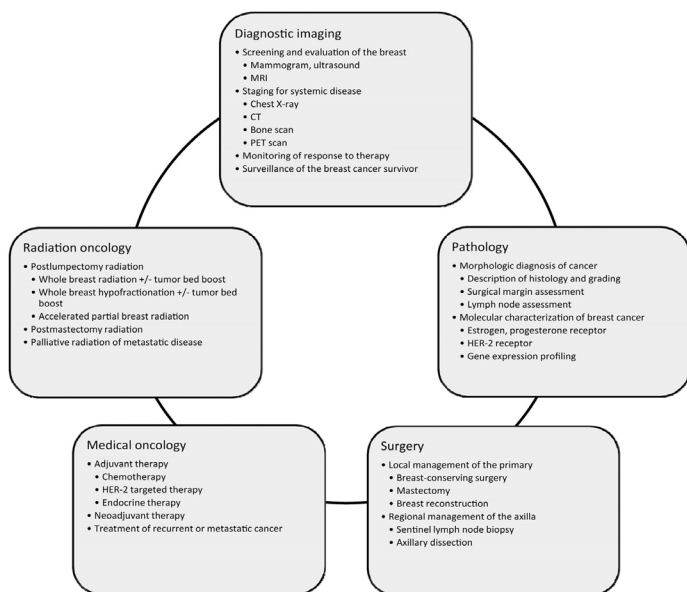


Figure 1: Courtesy ref no-6. Overview of multidisciplinary breast cancer management.

Methods

We conducted a review utilizing search engine PubMed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like surgery; presence or absence of Estrogen Receptor (ER); Progesterone Receptor (PR); Human Epidermal growth factor Receptor (HER2); Chemotherapy; Triple Negative Breast Cancer (TNBC); Endocrine therapy; Metastases; Radiotherapy; Imaging modalities; causes of TNBC; drug resistance; prognosis; markers for TNBC; effective tamoxifen; negative neo adjuvant chemotherapy; gene markers; role of microRNAs, from 1980's till august 2021.

Results

We found a total of 442800 articles out of which we selected 85 articles for this chapter on update on brear cancer management. No meta-analysis was done.

Breast cancer (BC) diagnosis

Screening

Breast cancer gets usually diagnosed via either screening or symptom (like pain or a mass that can be palpated) which stimulates a diagnostic evaluation. Screening of healthy women is correlated with the tumors getting picked up that are smaller, possess a lesser chances of metastases, have greater chances of Breast conserving along with restricted axillary surgery, with lesser likelihood of needing chemotherapy [7]. This type of clinical scene can translate to reduction in treatment associated mortality along with escalated survival.

The lone screening approach that has had evidence of reduction in Breast cancer associated mortality is mammography [8]. Screening mammography results in a 19% total decrease in Breast cancer associated mortality [3], possessing lesser advantage for women in the age group of 40's (15%), whereas greater advantage for women in 60-'s (32%). Secondary to that the Screening mammography is advocated by the American Cancer Society, initiating at age 45, or earlier based on individual choices. The probable negative features of screening mammography are false positive evaluation, exposure to radiation, pain, anxiety in addition to other negative psychological actions. There is 61% chances of false positive outcomes with mammography in a duration of 10yr for women initiating screening among the ages of 40yrs as well as 50yrs. These chances of false positive start undergoing reduction as the patients are of elder age [9]. US Preventive service Task force quoted a 15% Breast cancer associated mortality decrease in women 39-49yr age with mortality associated advantages from screening among the ages of 39 in addition to 69. Nevertheless, the Task force liberated a contradictory report that documented only biennial screening mammography for women in 50-74 age group, that excluded a large younger women maximum in view of high amount of false positive outcomes [10]. Mammography among women in 39-49yr age group was advocated if indicated following the utilization of risk-dependent model for Breast cancer screening, like the models generated by the population-dependent Research Optimizing Screening Through Personalized Regimen Network [11], or if asked by the patient.

Digital breast Tomosynthesis getting introduced subsequent to conventional full digital field mammography evaluation screening reduction of false positive outcomes, besides escalated cancer getting picked up [12]. The botheration of addition of Digital breast Tomosynthesis to screening is the rough doubling of the radiation dose over as well as above the total digital field mammography by itself [13]. For taking care of these problems, certain institutions try to reconstruct the synthetic 2dimensional (2D) images for 3D tomosynthesis images [13]. Early clinical experience with synthetic 2D images has illustrated no escalation in recall evaluations to ensure that the maximum synthetic advantage are sustained [14]. Despite that the decrease in false positive outcomes following the utilization of tomosynthesis has not been greater than modest (16/1000) [12], in addition to practice alterations like a lesser major recall of 9-10% (at present it is 12%) as well as escalation in the biopsy threshold from a 2% risk of malignancy [15] might have more implication in reduction of harm from screening.

Supplementation of mammography with rest of imaging methods for the patients at greater risk causes the extra pick up of Breast cancers that appear occult on mammography. A meta-analysis of 14 studies of patients possessing at greater risk BC

observed that Magnetic Resonance Imaging (MRI) possessed a greater sensitivity for malignancy (84.6%), or ultrasound (39.6%) [16]. Moreover the utilization of MRI as an add on to mammography possessed a greater sensitivity for malignancy (92.7%) in contrast to the utilization of ultrasound as a supplement to mammography (52%) [17]. Secondary to this women possessing lifetime chances of Breast cancer of over 20%, breast MRI works as add on to mammography is advocated by the American Cancer Society. This group inclusive of women possessing genetic mutations, that point to an escalation of chances of breast cancer, besides those possessing a history of radiation for therapy of breast cancer or for Hodgkin lymphoma, which included breast tissue. Ultrasound is a good alternative for the screening of patients possessing at greater risk BC who can't get a MRI done, or women possessing intermediate risk, like the ones with dense breasts. The basic restriction of screening ultrasound are a greater chances of false positive outcomes, besides dependent on the experience of the operator [18]. The greater chances of false positive outcomes (in addition to low anticipative value) of ultrasound has not met the least standards advocated by the ultrasound agency for health care Policy as well as Research [19]. With regards to other screening methods, of which few are detailed later, the present American College of Radiology appropriateness criteria say, that there is not enough proof for the use of extra/adunct screening imaging methods like a thermography, breast particular gamma imaging Positron Emission mammography, in addition to optimal imaging [20].

Pathologic analysis

A processing of specimens as well as analysis

In the Clinical scenario, tissue that is diseased is mostly derived by fine needle aspiration, core biopsy, or surgical removal. A challenge with regards to diagnosis is to separate from intricately correlated diseases, like atypical ductal hyperplasia along with in situ disease in addition to microinvasion, or ductal cancer. Utilization of auxiliary immunohistochemical along with molecular investigations can be done for aiding in properties of equivocal morphology in a lot, although not all the subjects. Characteristic like tissue handling, ischemic duration, cautery, utilization of frozen sections, fixation, decalcification in addition to processing, all are key for the quality of the histological sections utilized for microscopic analysis in addition to supporting investigations, like Immunohistochemistry (IHC), in situ hybridization, along with molecular investigations dependent on reverse transcription polymerase chain reaction.

The size of the tumor gets detected by proper physical, clinical as well as pathologic association. Once a breast cancer generates a separate mass outward from a point of origin, the size can get evaluated with great ease by imaging along with pathologic analysis. If the tumor originates in a badly defined field of genetic instability, besides existence of intra tumoral normal tissue, precise size determination might prove to be a big challenge. Additionally, detecting as well as precisely estimating small cancers by utilization of advanced imaging might be tough if they can't be sighted on gross inspection of the specimen, particularly in view of the surgical specimen that the pathology receives laboratory might deviate markedly from the in vivo shape seen by the surgeon as well as radiologist screening to elasticity of the breast tissue, surgical specimens are classically marked with ink in 6 dimensions as per the orientation described by surgeon. Nevertheless, margin evaluation following surgical removal is complicated by the absence of marking standardization, besides probable artifacts from cautery or

specimen handling.

Tumor markers that can anticipate

Key decisions on treatment are dependent on the protein expression, assays which are independent of tumor morphological properties. IHC evaluation of paraffin sections is conducted in routine for Estrogen Receptor (ER) - Progesterone Receptor (PR), and Her-2/neu (Human Epidermal growth factor Receptor; HER2) status. Despite the utilization for these are done in routine for anticipation of reactions to the targeted agents, histological tumor markers possess their restriction secondary to significant intra tumoral differences, in the same biopsy as well (figure2). RNA as well as DNA can further be examined in routine paraffin embedded tissue samples, in addition to detection by in situ hybridization of HER2 amplification in the form of a confirming investigation for IHC or as a stand alone assay (figure2, bottom right). A lot of stress is in rest of actionable targets in cancers genomes for precision treatment with utilization of next generation gene sequencing [21].

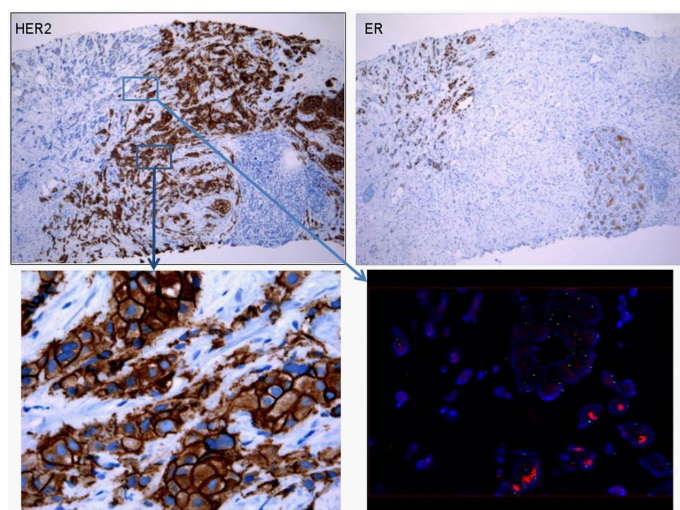


Figure 2: Courtesy ref no-6-Invasive mammary cancer with heterogeneity of predictive marker staining. (Top left) IHC shows intense HER2 staining in some sections of tumor. (Top right) On adjacent section, IHC shows ER-negative staining of HER2-positive cells and ER-positive staining of HER2-negative cells. (Bottom left) Higher-power view of HER2 staining. (Bottom right) Fluorescence in situ hybridization for HER2 at interface of HER2-positive and HER2-negative cells also demonstrates signal heterogeneity. This patient was treated with chemotherapy and trastuzumab. Posttherapy histology demonstrated robust viable tumor that was exclusively HER2-negative (not shown).

DNA microarrays in addition to high throughput reverse transcription quantitative real time Polymerase Chain Reaction (PCR) assays for a lot of genes (like 21 in Oncotype (Genomic Health Inc) along with 70 in Mamma Print [Agendia] can be utilized for clubbing of breast cancers into various prognostic groups [22]. Utilization of gene assays is done for anticipation of the chances of distant recurrence in early stage Breast Cancer (BC) in addition to implicate decisions in the context of systemic therapy. These investigations depend significantly on the evaluation of ER along with proliferation associated genes, like Ki-67, that have mostly overcome the utilization of other single markers of risk utilized in clinical scenario. Despite that the expression of ER along with PR might be heterogenous, besides the cellular proliferation status might differ in a single tumor (Figure3). In view of any biopsy sample gets exposed to sampling error in addition to sectioning of the full tumor for the

evaluation of anticipated in addition to prognostic biomarker is not practical, imaging for breast cancer biomarkers might have a key role in yielding a global overview of gene expression. Besides the biomarkers detailed earlier in addition to other cancer biomarkers along with oncogenic molecular genetic aberrations have got documented [23]; nevertheless, no unanimously agreement is there in view of constant alterations of standard of care, secondary to persistent standardization of the evaluation, assays protocols in addition to evaluation methodologies [24].

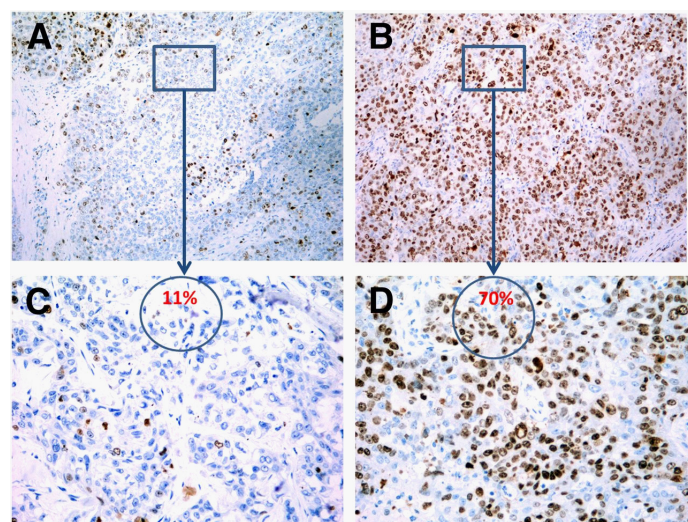


Figure 3: Courtesy ref no-6-Triple-negative invasive breast cancer demonstrating variations in proliferative status. (A and B) Two low-power views of Ki-67 IHC staining in single section from triple-negative tumor biopsy. (C and D) Higher-power (20 \times) views with calculation of representative Ki-67 scores (11% and 70%). Ki-67 scores were highly variable, even though these images were obtained from the same slide.

Imaging as well as staging

Physical examination, mammography, or the ultrasound for the diagnostic work up of a patient with newly diagnosed BC is generally enough for local regional staging. Magnetic Resonance Imaging (MRI) is occasionally advocated, particularly in a younger patient, a genetic mutation or in case of suspicious multifocal disease, or a mammogram or ultrasound is believed to be giving indeterminate observation. Despite the ability of MRI for detection of extra disease in the contralateral breast in about 3% of the time [25], meta-analysis of preoperative breast MRI have demonstrated an escalation in the rate of mastectomy [26], along with no local enhancement in local regulation following Breast Conserving Surgery (BCS) in addition to radiotherapy [27]. Breast MRI studies have demonstrated, chances of over determination of the tumor size [28]. Moreover, it is feasible that small extra chances estimated by MRI might never have clinical significance or be the cause of a local recurrence in view of adjuvant systemic or whole breast radiation therapy. MRI might possess a significant part in analyzing disease degree in case of greater restricted radiation to the tumor bed or just regional node gets irradiated is taken into account [29]. Additionally breast MRI can be done in patients getting neo adjuvant chemotherapy to evaluate the reactions along with contribute in surgery planning.

A clear radiograph in addition to routine laboratory blood tests are enough for staging in a patient with clinical stage I or II breast cancer in addition to no particular symptoms of met-

astatic disease. In case of suspicious advanced disease (stage III B/C or IV) disease National Comprehensive Cancer Network (version 1.2015) advocate either chest, abdomen, as well as pelvis CT or chest CT with abdomen as well as pelvis MRI in addition to bone scan or, utilization of sodium fluoride PET/CT using 2-deoxy-2-Fluoro-D-Glucose (18F FDG)/ Positron Emission Tomography (PET)/ Computed Tomography (CT). 1On 18F FDG/ PET/CT is associated as an optional for evaluation of stage IIIB/C or IV disease but has no indication for staging of stage I or II disease. Corroborating the utilization of PET for evaluation of advanced BC, a meta-analysis of 5 studies (n=547 patients), illustrated a sensitivity for BC, a of 0.97(95%CI, 0.93-0.99) along with as well as specificity of 0.95(95%CI, 0.90-0.97) [30].

Treatment of breast cancer

Surgery

The primary ways of local in addition to regional breast cancer treatment continues to be surgical intervention. In the initial half of 20th century William Stewart Halsted in 1894 Breast Conserving Surgery (BCS) got introduced by Fischer et al. [31] as well as Veronesi et al. [32], who documented that survival with lumpectomy along with breast radiation was equivalent to that with mastectomy in the therapy of early breast cancer. Enhancement in BC Screening has resulted in the diagnosis of impalpable tumors, that emphasizes on the requirement of a localization strategy for surgical management.

A. Breast conserving surgery (BCS)

Wire localization of the breast tumor remains the mainstay for BCS. The procedure gets done by the aid of a breast imaging radiologist on the day of surgery. Surgical incision over the breast gets guided by keeping in mind cosmetic angle besides the area where the tumor is situated. Ideal is a circumareolar incision for a tumor located 1-2cm from the areolar margin, nevertheless, for a tumor exists at a >2cm distance from the areola, placing the incision directly over the concerned region might be beneficial, in case lumpectomy site can be identified with ease in case a margin reexcision is required. Following the incision, the length of the localization needle registered along with dissection can occur just directly over at the needle track.

Radioactive seed localization results in reduction of the time the patient spends in the hospital on the day of surgery along with aids the surgeon for placement of the incision over the region with the maximum counts without needing to account for the site from where needle entered, that may lie in a quadrant separate in contrast to the tumor. Studies that contrasted radioactive seed localization from the Wire localization illustrated no significant variation in operating duration with a probable lesser reexcision rate with the seed localization method [33].

Women possessing large breasts, wide excision can be done with the utilization of an oncoplastic method, that mostly implicates breast reduction. Silverstein et al. [34], launched this strategy for the management of in situ breast cancers with the aim of getting surgical margins of greater than 1cm in addition to preventing whole breast radiation therapy [35]. One warning for this procedure is in case positive margin exists, then reexcision might be tough in view of remodeling of tissue planes during the surgery. Hence patients need to be counseled prior to making a choice of this method, that a total mastectomy might be essential if clean pathologic margins (like no invasive breast cancer on ink or DCIS greater than 2mm from ink) are not received.

B. Non breast conserving surgery strategies

For maximum women where it is early stage breast cancer, in addition to has been diagnosed by Screening, mastectomy is a choice. Nevertheless, mastectomy might be essential for women that might have had received radiation to the side involved (for earlier breast cancer or Hodgkin lymphoma) or for women possessing comparatively smaller breasts in the background of a large primary breast cancer, massive calcifications, or in case of multicentric disease, neo adjuvant chemotherapy might downstage the primary cancer along with make breast conservation feasible.

Maximum women who opted for mastectomy are the ones who require reconstruction as early as feasible [29]. The surgical strategy varies for women who do not opt for reconstruction, with a greater ellipse of the skin needs removal. For the women who are getting a fast reconstruction, skin sparing mastectomy, with or without nipple conservation might be carried out. Nipple sparing mastectomy is mostly oncologically safe for in situ or stage I as well as II invasive breast cancers [36]. Certain parameters that anticipate nipple implication are the tumor size >5cm, spacing of the tumor to the nipple of <2.5cm, negative ER along with PR status with positive HER2 status [37]. Patients possessing malignant calcifications that had been projecting to upto 2cm of the nipple or inflammatory breast cancers are usually counseled against this method.

C. Axilla stage procedure

One of the main advances in breast cancers surgery in context of technology is the Sentinel Lymph Node Biopsy (SLNB) getting introduced for replacement of the conventional axillary lymph node dissection as detailed by Guiliano et al. [38], in 1994. SLNB is correlated with a significantly lesser lymphedema risk <2%-3% in contrast to total axillary lymph node dissection (15-20%) [39]. This strategy possesses over 80% precision, in case results are negative, in addition to no further, need of dissection. In case SLNB outcomes are positive, total axillary lymph node dissection has no utility for enhancement of local regional regulation or survival in women who don't possess any palpable adenopathy, 1 or 2 positive sentinel lymph node's, in addition to no gross extra nodal extension as illustrated by a large escalated Randomized controlled Clinical Trial (RCT), (American College of Surgeon's Oncology Group Z0011 trial) [40]. Breast radiologists usually conduct fine needle aspiration on non-palpable axillary lymph nodes, along with suspected imaging morphology. Having the knowledge of the Z0011 trial [40], this strategy creates a surgical conflict in the management of the axilla in view of maximum, of the implicated patients would have possessed the eligibility for SLNB. Whether these patients need to undergo total axillary lymph node dissection following positive fine needle aspiration outcome or if they still need a SLNB, in case the axillary outcomes are negative Clinically ?. These queries need further evaluation.

Utilization of SLNB might be done in clinically node positive patients following a good reaction to neo adjuvant chemotherapy, with a few cautions. The ACOSOG Z1071 trial illustrated that SLNB is possible following neoadjuvant chemotherapy, with a total false negative outcomes of 12.6% [41], A reduction in false negative outcomes occurred to 10.8%, in case when both radio-tracer along with blue dye were utilized as well as to 9.1% in case where a minimum of 3 sentinel lymph nodes was there [41]. During the SENTINA trial [42], one arm possessed patients, that transformed from clinically node positive to negative out-

comes for the axilla subsequent to neo adjuvant Chemotherapy (arm C) in addition to went through SLNB followed by total axillary lymph node dissection. The total chances of false negative outcomes of SLNB was 14.2% in case lymphatic mapping was conducted by either utilization of radio colloid or with blue dye injection. Nevertheless, a subset evaluation documented that the rate of false negative outcomes was significantly reduced in case both radiocolloid as well as blue dye got utilized in addition to when a where a minimum of 3 sentinel lymph nodes were excised (7.3%).

Medical oncology

Various wide classes of agents are present for the treatment of breast cancer; the properties of the tumor along with disease extent that decide the whether systemic chemotherapy, endocrine therapy or HER2 -oriented therapy. For early stage breast cancer, these factors are ER, PR, in addition to HER2 status. i) Lymph node having been implicated or not. ii) Size of the tumor. In case of stage IV disease the receptor status, besides the areas of metastases remain the major parameters.

A. Chemotherapy

Adjuvant chemotherapy following definitive surgery is usually advocated for the patients presenting with high chances of recurrence. These particular clinicopathological properties might be the indications for chemotherapy i) Triple negative breast cancer (TNBC or absence of ER, PR, HER2). ii) HER2 positive. iii) Greater tumor size. iv) Positive lymph nodes. Regarding those that are negative for lymph nodes in addition to ER positive tumors, RNA-dependent genomic testing utilization can be done for better prediction of the chances of distance recurrence in addition to pick up the patients who will gain advantage maximum from chemotherapy [43]. Genomic testing might also be brought into considerations, in case of patients possessing a restricted amount of positive lymph nodes following SLNB or total axillary lymph node dissection to estimate if chemotherapy is required [44]. In case of patients possessing high risk disease, cytotoxic therapy needs to be inclusive of anthracycline along with taxane. Once there is low risk disease, there are greater chances of anthracycline not being included. Deciding chemotherapy needs to be dependent on a balance of the potential survival advantage, keeping in mind the patients comorbidities in addition to the chances of complications.

B. HER2 aimed therapy

In case of HER2 positive breast cancer, trastuzumab, a HER2 particular monoclonal antibody, causes enhancement of the survival of patients with early stage breast cancer as well as needs to be given along with chemotherapy [45]. In view of the escalated chances of Heart Failure (HF), with anthracycline along with trastuzumab-possessing regimens non anthracycline, taxane possessing regimens can get utilized [46]. None of the trials have contrasted the different HER2 regimens, hence for the patients with the maximum risk, a standard regimen possesses an anthracycline followed by taxane along with trastuzumab. Irrespective of which chemotherapy gets utilized, trastuzumab needs to be persisted for a year [47], along with cardiac monitoring 3monthly. Further clinicians can also think of utilization of pertuzumab-a monoclonal antibody that gets directed to a separate area on the HER2 receptor in contrast to trastuzumab. The outcomes of NCT01358877, a phase III, double blind, placebo controlled trial, where patients with HER2 positive along with lymph nodes got randomized to get adjuvant pertuzumab

or placebo in addition to standard adjuvant chemotherapy as well as trastuzumab, are pending.

Endocrine therapy

Patients with ER, or PR positive breast cancer need to get endocrine therapy like aromatase inhibitors. In case there is botheration about enhancement of chances of osteoporosis or aromatase inhibitors being intolerated, then tamoxifen prescription can be used. Up till recently utilization of tamoxifen was done for all post menopausal women. Nevertheless, the outcomes of the randomized-3 arm SOFT trial pointed that ovarian repression in addition to exemestane proved superior to tamoxifen, nevertheless, just in women who got chemotherapy as well [48]. In view of chemotherapy getting delivered at the whims and fancies of the treating clinician, he advantage of ovarian repression along with exemestane was seen in the patients possessing the maximum chances of relapse (HER2 positive, greater tumor size positive lymph nodes). In case of pre menopausal women who do not get chemotherapy delivered, tamoxifen by it is acceptable. Not astonishingly, tamoxifen has better tolerance in contrast to ovarian repression along with exemestane, despite it be just for 2yrs. Endocrine therapy is being advocated for a minimum 5yrs, nevertheless, the outcomes of the randomized ATLAS study pointed a 3% extra enhancement in mortality from breast cancer with 10yrs consumption of tamoxifen instead of 5 [49].

Neoadjuvant chemotherapy

There exist a different types of indications for neoadjuvant chemotherapy i) A tumor over 5cm in patients wanting breast preservation. ii) A tumor fixed to the chest wall. iii) Locally advanced disease. iv) Inflammatory breast cancer.

Chemotherapy regimens are based on the receptor subtype- for maximum it would be anthracycline in addition to taxane. For the HER2 positive BC, trastuzumab along with pertuzumab need to be administered simultaneously with the taxane [50]. For the ones with locally advanced disease, where chemotherapy will be very toxic, yet still possess a breast cancer that can be cured, neoadjuvant endocrine therapy can further be thought off [51].

Treatment for metastatic disease

In view of metastatic disease is believes to be incurable, the aim of treatment is to prolong life, whereas reduction of symptoms or adverse actions to the minimum. Those patients with ER, or PR, positive HER2 negative breast cancer, mostly get endocrine therapy, a lot of times before being started single agent chemotherapy. Recent results validates the utilization of palbocicib, (an oral inhibitors of cyclin-based kinase 4 as well as 6) in addition to first line letrozole [52], along with 2nd line fulvestrasnt [53] in patients with ER positive metastatic disease. Those with HER2 positive metastatic BC need to get a taxane in addition to trastuzumab along with pertuzumab as 1st line treatment [54]. Later treatments might implicate use of trastuzumab-emantine [55], lapatinib, or trastuzumabwith other single agent chemotherapeutics. The only class of agents that are present for TNBC or absence of ER, PR, HER2 is chemotherapy.

Irrespective of what treatment gets decided ,the reaction to therapy in patients with metastatic disease need to be evaluation at predefined intervals by clinical along with imaging studies inclusive of CT. Bone scan, or PET/CT.

Radiation

Prospective randomized trials have validated that long term mortality from breast cancer along with total patient survival can be contrasted with BCS in addition to radiation therapy as well as for mastectomy [56]. BCS in addition to radiation therapy is also correlated with significantly greater local regulation rates (90-95%) in the conserved breast within 10yrs from therapy, with these rates being practically similar to those with mastectomy, with maximum women possessing a good or excellent cosmetic outcomes [57]. The low chances of local recurrence. In the modern day are secondary to the propagation in the multidisciplinary care of BC; i) Treatment of the disease initiate at earlier stage in view of early pick up secondary to screening. ii) enhancement of surgical methods ,besides pathology evaluation. iii) Enhancement of radiation methods, that might result in reduction in marginal mass, besides escalation of radiation dosage, with a tumor bed boost, when needed. iv) In addition to that chemotherapy or endocrine systemic therapies when indication exists are used widely. Radiation further has illustrated part in the therapy of stage 0 breast cancer (ductal carcinoma in situ). v) 90-95% long term local regulation gets accomplished with enhanced patient selection in addition to surgical as well as radiation methods [58].

Marked advances in the delivering of post operative radiation has been witnessed in the past decade with the objective of maximum ideal treatment as per the patient's anatomy, with reduction in acute or long term toxicity. 3Dimensional (3D) planning with the utilization of CT stimulator as well as either field in field 3D conformal therapy(or forward planning) or intensity modulation radiation therapy (alias inverse planning) has taken over from the simple 2D planned breast tangents. By reduction of the dose non homogeneity, these advances in the method have a correlation with lesser chances of complications, like acute skin desquamation, oedema, late fibrosis or negative cosmetic actions on the breast [59]. Additionally, methods implicating utilization of prone position, besides deep breathing coordination of breath holding are utilized now besides getting utilized for left side breast cancer or large size for reduction of toxicity (Specifically cardiac dose sparing) [60].

A. Radiation following breast conserving surgery (BCS)

Randomized trials have validated the recurrence rates with just BCS in addition to radiation therapy, even for patients enrolled for favorable clinical along with pathological factors [61]. Additionally, a little survival benefit of radiation exists in patients possessing invasive breast cancer. Nevertheless, BCS without radiation might be a method for women who have got enrolled with care. In case of early stage invasive breast cancer, the combination of elderly age, tumor size on the smaller side, negative outcomes for lymph nodes as well as hormonal sensitivity have got correlated with a lesser risk of local recurrence following BCS without radiation [62]. In cases of ductal carcinoma in situ, BCS by itself might be a method for tumor size on the smaller side, possessing wider margins as well as low to intermediate grade [63]. Once patients who have got enrolled with care, subgroup of patients with these properties, might have low recurrence rate that can be acknowledged, despite no radiation (not having chances of significantly impacting the odds for survival. Trials have not persistently needed MRI staging that might enhance the picking up of extra foci that are existing far from the tumor bed, that might result in early recurrence in patients not getting radiation .

B. Radiation of regional nodes

Radiation therapy possesses a part in the regional regulation of nodal disease in a lot of patients possessing high risk disease or nodes positive stage II in addition to maximum patients with stage III breast cancer. The primary region that is possessing chances for regional recurrence in patients with positive axillary lymph nodes is the supraclavicular lymph node in addition to high axillary nodes with positive outcomes in contrast to those with negative outcomes, the degree of axillary dissection as well as massive lymphovascular invasion. Despite breast, FDG-PET/CT possesses low sensitivity for axillary disease (60%), this is very large specificity [64].

The part of elective radiation of the internal mammary chain continues to be contradictory following 50yrs of study. Studies of elective nodal radiation have either given negative outcomes or resulted in just a minimal disease free survival advantage [65]. Patient enrollment for internal mammary nodes radiation is usually advocated for subgroups possessing greater chances in view of internal quadrant tumor presence with positive axillary lymph nodes, massive lymphovascular invasion, or hormone receptor negative tumors [65]. The negative outcomes in these trials of elective radiation might partially have been secondary to the randomization of large quantity of patients without actual disease implication. Imaging might get utilized for selection of patients possessing nodal implication prior to any intervention (figure4), but this strategy utilization has not been done in prospective trials. PET/CT picks up hidden lymph nodes metastases in the internal mammary chain in about 10-15% of patients resulting in changes in radiation field selection in 10-16% patients [66].

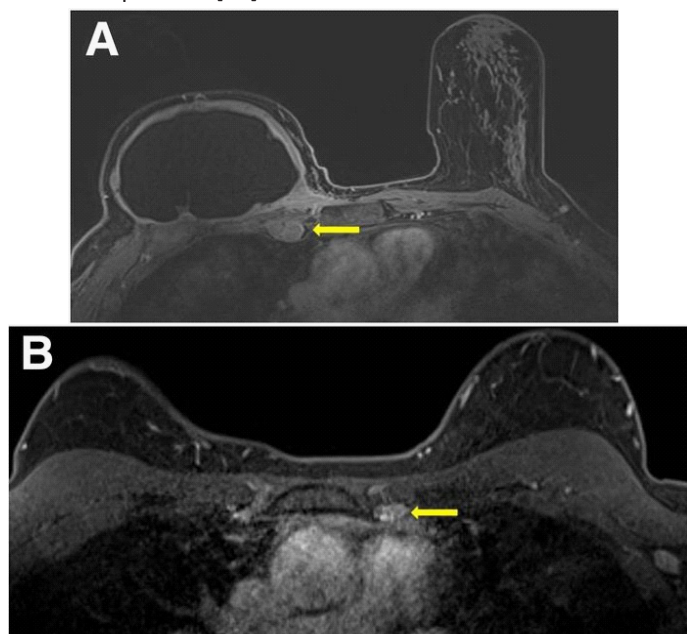


Figure 4: Courtesy ref no-6-Internal mammary node enlargement detected by breast MRI in 2 patients (A and B) Imaging detected abnormal internal mammary lymph nodes (arrows) on basis of size and enhancement.

C. Radiation in postmastectomy

In case of women receiving therapy with mastectomy, radiation is advocated for adjuvant therapy in the presence of clinical along with pathological factors that cause anticipation of an intermediate to a high risk ($\geq 10\%$) of local regional recurrence [67]. Randomized prospective trials have validated decrease in local regional recurrence as well as an enhancement in survival with radiation in post mastectomy

In this particular subgroups of women [68]. As compared to that, women possessing a low risk for local regional recurrence following mastectomy do not need radiation. Patients usually receiving radiation in postmastectomy are inclusive of those who possess 4 or greater positive axillary lymph nodes, T3 tumor size, resection margins are positive, along with locally advanced or inflammatory BC. Radiation is further advocated for patients possessing 1-3 positive nodes besides other parameters for local- regional recurrence, like massive lymphovascular invasion, younger case, high grade tumors, or hormone receptor negative BC[69].

D. Radiation length reduction

In the last decade a lot of advances have been encountered in the methods in the methods of administration of postoperative radiation possessing the objective of greater chances of local regulation but cause reduction of total time, cost as well as enhance ease of care. Hypofractionation by definition is the utilization of radiation therapy with lesser, bigger dosages in contrast to the conventional fraction sizes of 1.8-2Gy/d. Hypofractionated Whole Breast Radiation (WBI) proven as a Standard of care for the postlumpectomy radiation for early stage breast cancer, largely, in view of the beneficial 10yr outcomes of 4 prospective randomized trials done in UK as well as awa Canada [69]. These trials illustrated equivalent local regulation in addition to almost akin or might be even better cosmetic results along with late toxicities observed with hypofractionation. One of the hurdles with regards to greater agreement with WBI has been the lower continuation of in the 4 main trials of some subgroups of patients, like the ones under 50yrs age, as well as needing a boost of systemic chemotherapy. At present about 20% of women receiving WBI treatment [70]. The Radiation Therapy Oncology Group finished a phase III Randomized trial (RTOG 1005) of hypofractionated WBI with a concomitant boost having the aims of enhancement of the utilization of hypofractionation by recruiting a patient population wider in contrast to the presently recruited in the present hypofractionated WBI studies as well as further resulting in reduction of the treatment time in just 3 wks.

Accelerated Partial Breast Irradiation (APBI) is moving away from whole breast irradiation since just the area surrounding the primary tumor inclusive of a narrow margin, gets targeted with radiation. The main method that has utilization in APBI can be subdivided into i) External beam radiation therapy as well as ii) Administration of radiation via sources located inside temporary internal catheters (brachytherapy) [71]. In view of significantly smaller treatment volume, the dosage of the radiation is escalated along with the reduction in treatment duration, usually twice twice/day for 10 fractionation over 1 wk. Not all the patients possessing early stage breast cancer are suitable for APBI; in the last 5yrs outcomes, recruitment was usually restricted to patients possessing small tumor size in addition to beneficial histological properties. The extent to which young age or bad histological properties would implicate long term regulation with APBI is still uncertain. The National Surgical Adjuvant Breast and Bowel Project as well as the Radiation Therapy Oncology Research Group have finished a phase III randomized study (NSABP-39/RTOG0413)-1of the many world over which are waiting follow up as well as publication of outcomes -evaluation of the APBI; against whole breast radiation therapy with endpoints of local regulation, survival, cosmetic results as well as quality of life (QOL) [72].

Advances in management of TNMC resistant to Conventional therapies

Earlier we had reviewed the recent advances in management of TNMC resistant cases of BC. Triple Negative Breast Cancer (TNBC) refers to the absence of estrogen, progesterone and HER2 receptors, possesses an aggressive clinical nature, having the high metastases rates. Thus here in this review we have tried to study the mechanism responsible for the high metastases rates by studying the role of Haematopoietic Protein Tyrosine Phosphatases (HePTP) which had a crucial role in metastases of TNBC through activation of Wnt/ β -catenin signaling. Further we examined, how certain regional anaesthetics like ropivacaine and levobupivacaine had a protective effect in BC, roles of some novel therapies like those combining Embelin (EMB)/ TRAIL-HA (hyaluronic acid)/ poly (1,6-hexanediol)-diacrylate β -5-hydroxyamylamine(PBAE)-polyethylamine (PEI) as cytotoxic and proapoptotic agents against TNBC, how regulation of miR 122-5p that causes aggression via Epithelial Mesenchymal Transition (EMT) in TIMC via suppression of charged multivesicular body protein 3 (CHMP3) through MAPK signaling might help in controlling TNBC. Further combining thiosemicarbazone compound 4 with cisplatin increased p53 phosphorylation, along with Bax level induction, as well as a decreased Bcl2 protein amounts, increased PARP cleavage and modulated miR expression levels in TNBCs with special overexpression of miR-125a-5p, and miR-181a-5p and thus role of miR control utilization by other way by thiosemicarbazone compound 4 targeting TNBC apoptosis might be utilized. Moreover how combining Src inhibitor dasatinib, with the PARP inhibitor veliparib, and the DNA damaging drug carboplatin in TNBC might prove effective in TNBC. Further role of DDB2 in causing resistance to PARP, combination of PARP with metabolic inhibitors is discussed. Additionally liposomes modified by fructose and RGD had >potential for forming a targeted TNBC therapy, particularly the covalently modified Fru-RGD-Lip, marking them as good liposomes having multiple functions. Thus novel therapies for TNBC which might help in developing novel therapies further for controlling TNBC has been emphasized [73].

A. Role of PALB2

Partner and Localizer of BRCA2 (PALB2) is vital for Homologous Recombination (HR) repair in response to DNA Double-Strand Breaks (DSBs). PALB2 functions as a tumor suppressor and participates in the maintenance of genome integrity. Recently Wu et al. summarize the current knowledge of the biological roles of the multifaceted PALB2 protein along with its control. Moreover, they demonstrated an association among PALB2 Pathogenic Variants (PVs) and breast cancer predisposition, aggressive clinicopathological parameters, along with poor clinical prognosis. They also described both the opportunities and challenges which the identification of PALB2 PVs yields in breast cancer genetic counseling along with precision medicine [74].

B. Role of hydrogen sulfide (H₂S) in Cancer

Hydrogen Sulfide (H₂S), an endogenously produced gaso-transmitter, is involved in various significant physiological in addition to disease situations, inclusive of vasodilation, stimulation of cellular bioenergetics, anti-inflammation, and pro-angiogenesis. In cancer, abnormally up-regulated of H₂S generating enzymes is frequently seen in various cancer types. The

recognition that tumor derived H₂S has different parts at the time of cancer generation displays opportunities of targeting H₂S modulated signaling pathways in cancer therapy. Wang et al. reviewed, with Concentration on the mode of H₂S-modulated protein persulfidation and the detailed insight with regards to impairment the of H₂S-generating enzymes along with metabolism in various cancer kinds. They further gave an update on modes of H₂S-mediated cancer propagation in addition to summarized the present alternatives for modulation of H₂S generation for cancer therapy [75].

C. Role of hydrogen sulfide (H₂S) in TNBC

Hydrogen sulfide (H₂S) is considered as a novel second-messenger molecule associated with the modulation of different physiological and pathological events. In the field of antitumor research, endogenous H₂S stimulates angiogenesis, escalates the cell cycle and hampers programmed cell death alias apoptosis, which facilitates oncogenesis ultimately. Intriguingly, high amounts of exogenous H₂S released from donors repress the growth of different tumors through stimulation of cellular acidification in addition to modulation of different signaling pathways implicated in cell cycle control, proliferation, apoptosis along with metastasis. The selective liberation of some amounts of H₂S from H₂S donors in the target has been believed to work as an alternative tumor therapy strategy. Triple-Negative Breast Cancer (TNBC), that represents an aggressive subtype with less than one year median survival time, is known to account for approximately 15-20% of all breast cancers. Due to the absence of agreed targeted therapy, the clinical treatment of TNBC is still interfered by metastasis in addition to recurrence. Significant efforts have been spent on generation of innovative treatments of TNBC, and remarkable progress in the control of TNBC by H₂S donors and their derivatives have been made in reviewed years. Thus Lia et al. reviewed, besides summarizing different pathways implicated in antitumor and antimetastasis actions of H₂S donors and their derivatives on TNBC, which provides novel insights for TNBC treatment [76] (Figure 5,6).

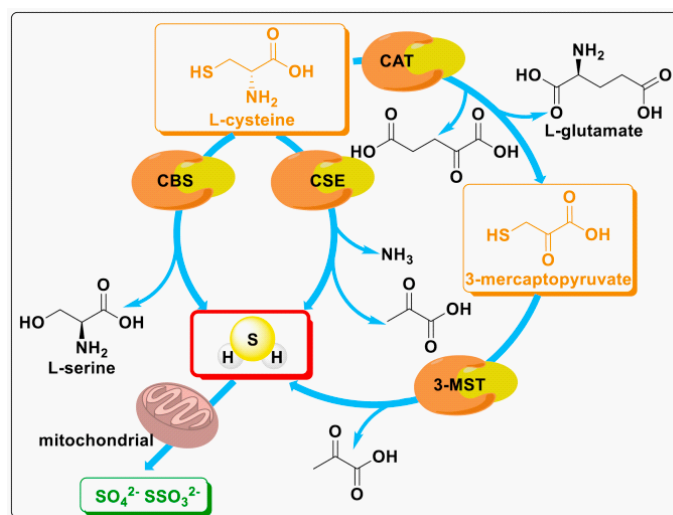


Figure 5: Courtesy ref no-76-Main mechanisms of endogenous H₂S production in mammalian cells. Endogenous H₂S can be produced mainly through three pathways. Among which, L-cysteine directly generates H₂S through the catalysis of CBS or CSE. H₂S is also biosynthesized by the synergistic effects of CAT and 3-MST. Ultimately, H₂S is metabolized in mitochondria in the form of thiosulfate or sulfate.

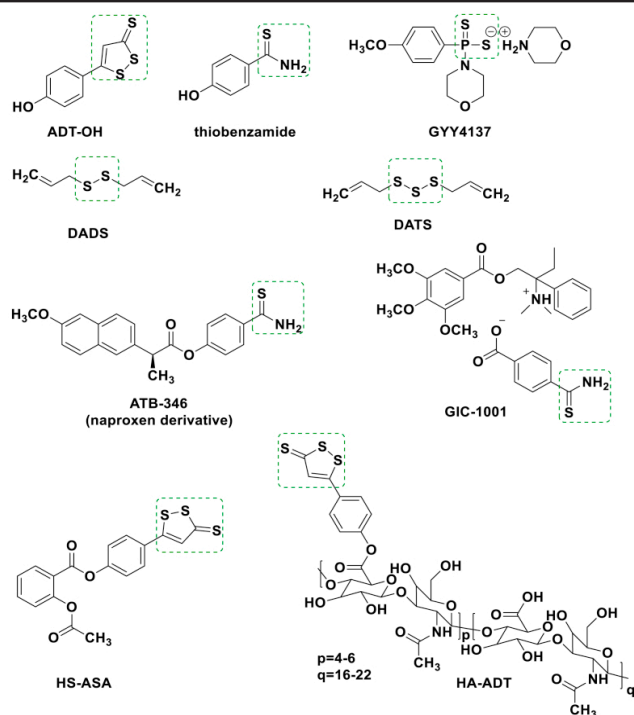


Figure 6: Courtesy ref np-76-Structural components of H_2S donors and H_2S generating drug candidates. Potential antitumor mechanism of H_2S donors against TNBC.

D. Role of microRNAs (miRNAs)

MicroRNAs (miRNAs) are emerging drivers in tumor propagation, whereas the part of miR-503-3p in breast cancer remains largely unknown. Huang et al., with the objective to evaluate the action of macrophage-obtained exosomal miR-503-3p in the generation of BC by controlling disheveled-associated binding antagonist of beta-catenin 2 (DACT2). miR-503-3p and DACT2 expression in BC tissues and cells were evaluated, in addition to the expression of Wnt/ β -catenin signaling pathway associated proteins in BC cells were further analyzed. Macrophages were induced and exosomes were extracted. The screened BC cell lines were, respectively, treated with exosomes, miR-503-3p hamper/simulate or upregulated/ hampered DACT2, along with the phenotypes, glucose intake, oxygen consumption rate, and Adenosine-Triphosphate (ATP) level of BC cells were checked. Cell growth in vivo was also observed. miR-503-3p was escalated, reduction of DACT2 was observed, with stimulation of Wnt/ β -catenin signaling pathway in BC cells. Macrophage-obtained exosomes, upregulated miR-503-3p or hampered DACT2 facilitated malignant behaviors of BC cells, glucose intake, and activity of the Wnt/ β -catenin signaling pathway, while repressed oxygen consumption rate and ATP level in BC cells. On the other hand, hampered as well as decreased miR-503-3p or upregulated DACT2 had an opposite impact. This study illustrated that decreased macrophage-derived exosomal miR-503-3p repressed glycolysis and promoted mitochondrial oxidative phosphorylation in BC by escalating DACT2 in addition to inactivation of Wnt/ β -catenin signaling pathway. Their research might give innovative targets for BC treatment [77].

E. In Doxorubicin (DOX) Resistance

Chemotherapy is one of the most common treatment options for breast cancer (BC) patients. However, about half of the BC patients are chemotherapeutic resistant. Doxorubicin (DOX) is considered as one of the first line drugs in the treatment of BC patients whose function is negatively affected by multi drug resistance. Due to the severe side effects of DOX, it is very im-

portant to diagnose the DOX resistant BC patients. Therefore, evaluation of molecular modes implicated in DOX resistance might escalate the clinical results in BC patients by introducing the novel therapeutic and diagnostic molecular markers. MicroRNAs (miRNAs) as members of the non-coding RNAs family have key parts in different cellular events inclusive of cell proliferation apoptosis. Hence, abnormal miRNAs functions and expressions can be associated with tumor progression, metastasis, and drug resistance. Moreover, due to miRNAs stability in body fluids, they can be considered as non-invasive diagnostic markers for the DOX response in BC patients. Zangouei et al., reviewed, besides summarizing all of the miRNAs that have been documented to be correlated with DOX resistance in BC for the first time in the world. In view of DOX possessing robust adverse actions, it is needed to separate the non DOX-responders from responders to enhance the clinical results of BC patients. This review highlights the miRNAs as key controllers of DOX resistance in breast tumor cells. Furthermore, this review paves tries to introduce non-invasive panel of prediction markers for DOX response among BC patients [78].

Role of immunotherapy

TNBC is a highly molecular heterogeneous disease that can be stratification, with Lehmann et al. [79]. Initially classifying TNBC into six subtypes-basal-like 1 (BL1), basal-like 2 (BL2), Immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and Luminal Androgen Receptor (LAR). Due to the absence of targets of hormone receptors and HER2, treatment of TNBC or advanced TNBC relies on conventional chemotherapeutic agents, but their effectiveness as well as prognosis are poor. In patients with advanced TNBC, poorer outcomes are seen. Recently, with the launch of clinical trials and advancements in molecular studies, targeted therapy for signaling transduction pathways, immunotherapy for immune checkpoints, and new chemotherapy strategies have provided feasible or potential therapeutic options for advanced TNBC. Earlier we had reviewed an article among Nutrients Competition in immunotherapy [80]. Thus Shi et al. [81] summarized the recent advances in targeted therapy, immunotherapy, as well as chemotherapy for advanced TNBC. Further Xing et al. [82]. Reported a high prevalence of TNBC in Shengai China [82].

Pregnancy following breast cancer treatment

In 2017 we reviewed a case report related to donor egg in Vitro Fertilization (IVF) following therapy for BC besides the problems implicated with chemotherapy with regards to pregnancy. With the recent advances in breast cancer treatment the 5-years survival rates have increased significantly with overall 20yrs survival in developed countries like USA. With further improvement being designed in the treatment of breast cancers with more and more sophisticated models to study breast cancer in human beings using the modern microfluidic models one expects more and younger breast cancer survivors to be needing fertility treatments. Here we review the modern advances in breast cancer treatments and the need for emphasizing on fertility preservation before starting any chemotherapeutic or other management as recommended by both ASO and ASRM. We further discuss the methods of fertility preservation in such young breast cancer patients or models without affecting there 5 years survivals we further report a case of HER2 positive breast cancer patient receiving multiple chemotherapeutic agents followed by radiotherapy where such treatment was not even discussed in a patient of primary infertility before starting treatment like chemotherapy and radiotherapy even in a devel-

oping country where cryopreservation of embryos or oocytes was possible just before the treatment if not preserving the ovarian tissue [83].

Recently, Perri et al. [84], reported no enhancement of risks in patients possessing BRCA1 or BRCA mutation, nevertheless, García-Planells et al. [85], did not agree with their results as well as advocated the following steps; mammography before the IVF cycle (preferably MRI with contrast) to pick up potential precancerous lesions, following the cycle during pregnancy between 4 and 6 months ultrasonography would be advocated. From clinical point perspective, the best treatment is an avoidable as well as screening approach. Expert opinion advocate women with BRCA 1/2 mutations need to undergo breast cancer screening with MRI, initiating at age 25 years, then mammography initiating at age 30 years, and ovarian cancer screening with pelvic examinations, ultrasonography, and CA-125 estimation. Surgical prophylaxis options for carriers of BRCA1/2 mutations include prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy. United States Preventive Services Task Force advocate biennial screening mammography for average risk women beginning at age 50 years and individualized screening decisions in women aged 75 years based on breast cancer risk [85].

Conclusions

Continuing analysis of breast cancer diagnosis in addition to management has caused a model shift from the standardized treatment regimens to precision medicine targeting the individual genetic composition of patients as well as tumors. Personalization of treatment of BC patients by integrating evaluation of standard immunohistochemical markers in addition to gene expression with knowledge from anatomic imaging in addition to targeted functional imaging studies for tailoring both planning of therapy along with reaction evaluation (Figure7).

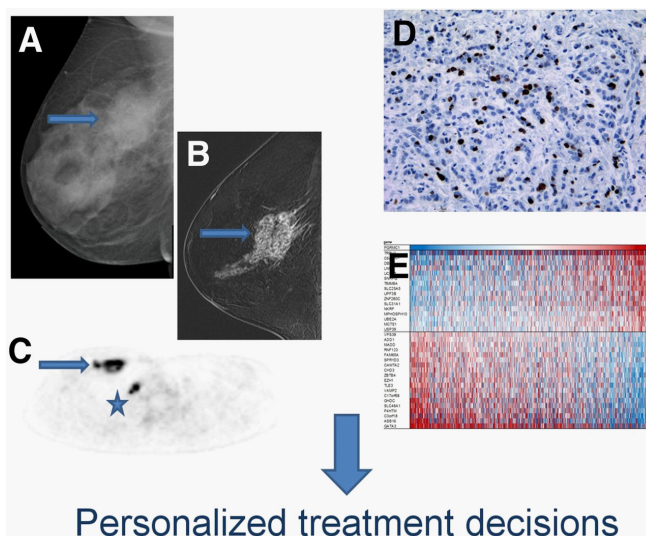


Figure 7: Courtesy ref no-6-Precision medicine is the future of cancer therapy. Structural and functional information from imaging is combined with immunohistochemical and genomic information to make personalized treatment decisions. (A) Breast cancer (arrow) is largely obscured on mammography. (B) Variable uptake of gadolinium contrast agent on breast MRI (arrow) indicates heterogeneity of intratumoral blood flow. (C) Variable uptake of ¹⁸F-FDG PET radiotracer (arrow) indicates heterogeneity of glucose metabolism in primary breast cancer. Extra axillary nodal disease is also demonstrated (*). (D) This information is combined with that from immunohistochemical assays, and mRNA expression (E) to determine a full tumor profile for treatment planning.

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