



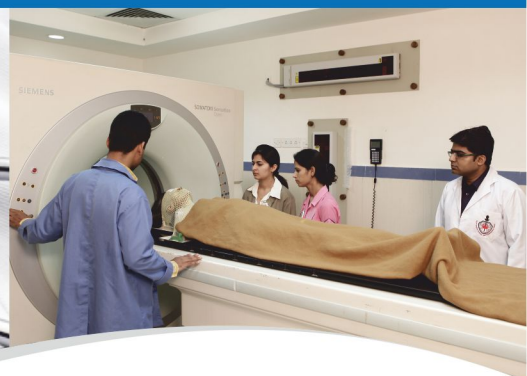
CANCER NEWS

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Focus Area:
BREAST CANCER



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From the Desk of Director Research

Cancer of the breast is an ancient disease. It was first described by the Egyptians three thousand years before the birth of Christ, at which point it was considered incurable. Fifty centuries later, more than one-third of women are cured. Nevertheless, it continues to be a major cause of mortality and morbidity.

Collectively, US, India and China account for almost one-third of the global breast cancer burden. In 2012 in India, 144,937 women were newly detected with breast cancer. Of these 70,218 women died an unprecedented rise in mortality in breast cancer cases across all sections of society. Cancer of the breast was followed by cancer of the cervix in all the twelve PBCRs, except, Barshi and Chennai where cancer of the cervix was followed by cancer of the breast. WHO prediction for the year 2015 indicates that there will be an estimated 1,55,000 new cases of breast cancer in India and about 76,000 women are expected to die of the disease. The gap only seems to be widening, which means, we need to work aggressively on early detection.

Risk factors for breast cancer include both modifiable and non modifiable variables. Only 5–10% of breast cancer cases are hereditary and for women with germline *BRCA* mutations, the breast cancer risk is substantial. Women with *BRCA* mutation-associated breast cancer also face elevated risk of second malignancy and an elevated risk of contralateral breast cancer. Rapid genetic testing for *BRCA1* and *BRCA2* mutations is now available at the time of breast cancer diagnosis and even as a part of initial screening programmes. *BRCA* mutation status can be considered when making treatment and prevention decisions for *BRCA* mutation carriers with breast cancer can be done. Other newer worrying factors include: age shift (more young ladies affected), late presentation (this directly decreases long-term survival of the patient), lack of awareness and screening (screening is the single most important factor responsible for better survival of patients in the west), aggressive cancers in young (generally, the younger the age below menopause, the more aggressive the cancer).

Cancer is a disease of the cellular genome, and therefore breast cancers are understandably characterized by abundant genetic diversity. Information about genetic alterations and protein expression level is considered along side histology in order to better comprehend the pathogenesis of breast cancer. Recent advances in the field of molecular-based cancer biology have revealed that identifying a gene signature, has led to the successful development and approval of targeted therapies. Therefore, molecular testing is now routinely used to guide clinical care of breast cancer patients to predict one's therapeutic response.

To date, introduction of next-generation sequencing technology offers the ability to detect high-throughput, and multiple genetic alterations in both constitutional and cancer genomes. Such advanced biotechnology has not only contributed in our understanding of breast cancer but has also unproved our ability to accurately discover the cancer genome.

Management of breast cancer is undertaken by a multidisciplinary team based on national and international guidelines. Depending on clinical criteria (age, type of cancer, size, presence or absence of metastasis), patients are roughly divided into high risk and low risk cases, with each risk category following different rules for therapy. Treatment possibilities include surgery, radiation therapy, chemotherapy, hormone therapy, and immune therapy. The mainstay of breast cancer treatment is surgery when the tumor is localized, followed by chemotherapy (when indicated), radiotherapy, and for estrogen receptor -positive tumours, adjuvant hormonal therapy (with tamoxifen or an aromatase inhibitor).

The present issue of the Cancer News highlights the newer advances in the field of "Breast Cancer" and features regular articles, such as Special Feature, Guest Article, Perspective and In Focus. We are grateful to Dr Amit Verma, Consultant Molecular Oncology and Cancer Genetics, In-Charge "Familial Cancer Clinic" Max Cancer Center for the "Guest Article"; Dr Urvashi Bahadur, Director, Medical Genetics and Genomics and Dr Shreya Paliwal, Senior Scientist, Clinical Genomics for "In Focus".

Suggestions/ comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

MANAGING THE AXILLA IN EARLY BREAST CANCER IN THE GENOMIC ERA : SLNB & BEYOND

Introduction

For over a century, Axillary Dissection has been the gold standard in the management of axilla in breast cancer. The nineties saw the evolution of sentinel lymph node biopsy with the pioneering work of Morton (1991), Krag (1993) and Giuliano (1994). Since then, there has been a paradigm shift in the management of clinically N0 Axilla. The western world has been prompt in the adoption of SLNB in early breast cancer. The NCCN recommends that SLNB should be the preferred method of surgical axillary staging.

In India and other developing countries, there has been a revolutionary rise in the number of women presenting with early breast cancer owing to increasing awareness and technologic advances in healthcare system. The oncological fraternity in India is readily gearing up for managing the N0 axilla.

Approach to the Axilla

Cancer surgery has been traditionally defined by radical resection with clear margins and regional lymph node dissection. Lymph node dissection determines staging, contributes to local control and perhaps translates to survival benefit. So also axillary dissection has been an integral component of modified radical mastectomy. But ever since the halstedian era there has been a

revolutionary change from radical to conservative approach. A comprehensive axillary dissection may be justified in a clinically node positive axilla.

In a clinically N0 axilla, the possibility of lymph node positivity in final HPE is 20-30%. In the rest of the 70-80% of the patients, comprehensive axillary dissection is probably an overtreatment. Axillary recurrence post ALND is about 1%. A recent meta analyses¹ failed to demonstrate a survival benefit for ALND in cN0 patients with early breast cancer. Moreover, the early and late complications of ALND include erythema, seroma, shoulder dysfunction, damage to neurovascular structures, lymphedema, pain & paresthesia.

Observation on the other hand is under treatment with axillary relapse rates as high as 15%–37% which is reduced to <5% by radiotherapy.

Staging a N0 axilla is comprehensive and includes clinical examination, imaging and surgery. Clinical examination is least accurate in staging axilla. USG, MRI & PET have been studied for preoperative evaluation of the axilla. But none of the imaging modalities have been proved to be accurate enough for staging the axilla.

Sentinel Lymph Node Biopsy

Attempts to identify the sentinel lymph node or the first lymph node in the lymphatic hierarchy to harbor tumor by various groups became successful. Cabanas² was the first to describe the sentinel lymph node in the lymphatic drainage of penis. Morton worked on colloidal gold to elucidate lymphatics in cutaneous melanoma. Giuliano³ in 1994 came up with blue dye mapping in breast cancer. Even though the concept of sentinel lymph node was introduced for melanoma it has been

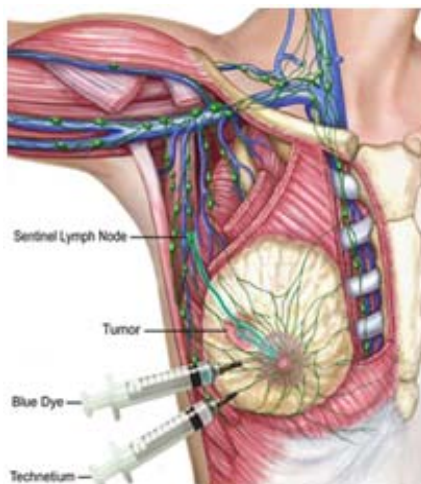


Fig 1: Sentinel lymph node biopsy

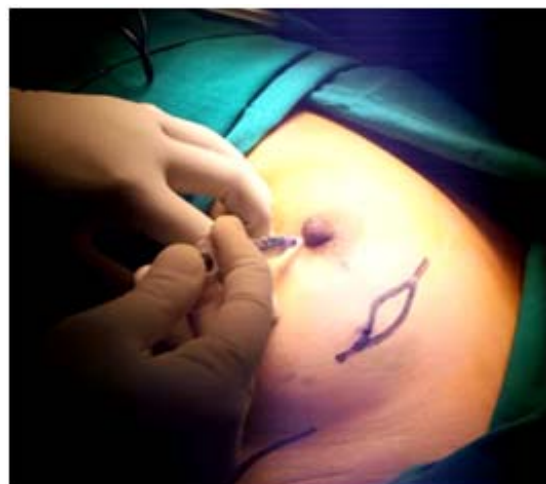


Fig 2: Blue dye technique

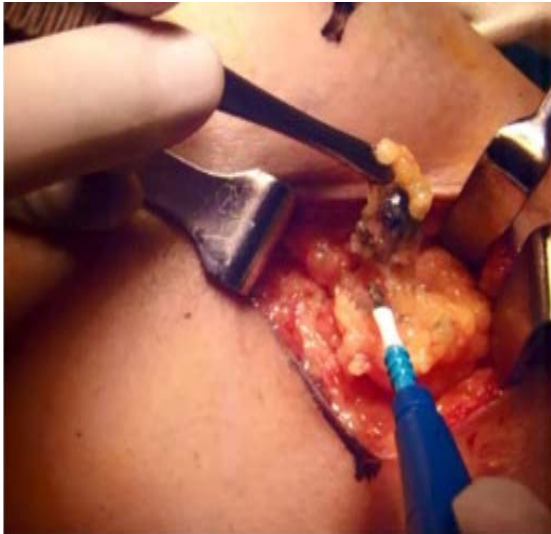


Fig 3: Sentinel node identification

extensively studied and validated in early breast cancer with clinically negative axilla. More than 60 studies validated by a back up of ALND confirms the overall success rate of 96 % and a false negative rate of 7 %.

Techniques of SLNB

The various techniques for sentinel lymph node biopsy are:

Dye Technique: Various blue dyes have been studied extensively and found safe and effective for SLNB. Isosulfan blue has been recommended for routine use of SLNB. The blue dye is injected intraoperatively just after induction either in subareolar or periareolar location. After 10-15 minutes, axillary incision is given and the sentinel lymph node is identified as the blue node. Sometimes more than one blue node is identified. The



Fig 4: GM counter

blue nodes are harvested and sent for frozen section. If negative then it is unlikely that other axillary lymph nodes harbor metastasis.

Radiocolloid Technique: In the radiocolloid technique radioactive technetium is injected few hours before surgery. Preoperative lymphoscintigraphy confirms the uptake in the sentinel lymph node in the axilla. Then intraoperatively the axilla is explored. The sentinel lymph node is identified as the hot node with the help of a Geiger Muller counter that traces radioactivity. The hot node is harvested and evaluated by frozen section.

Combined Technique: In the combined technique, both the blue dye and radiocolloid is used. The blue and hot nodes are dissected and evaluated for metastasis. The combined technique has been found to be more effective than either the dye or radiocolloid alone.



Fig 5: Axillary clearance



Fig 6: Lymphedema left upper limb

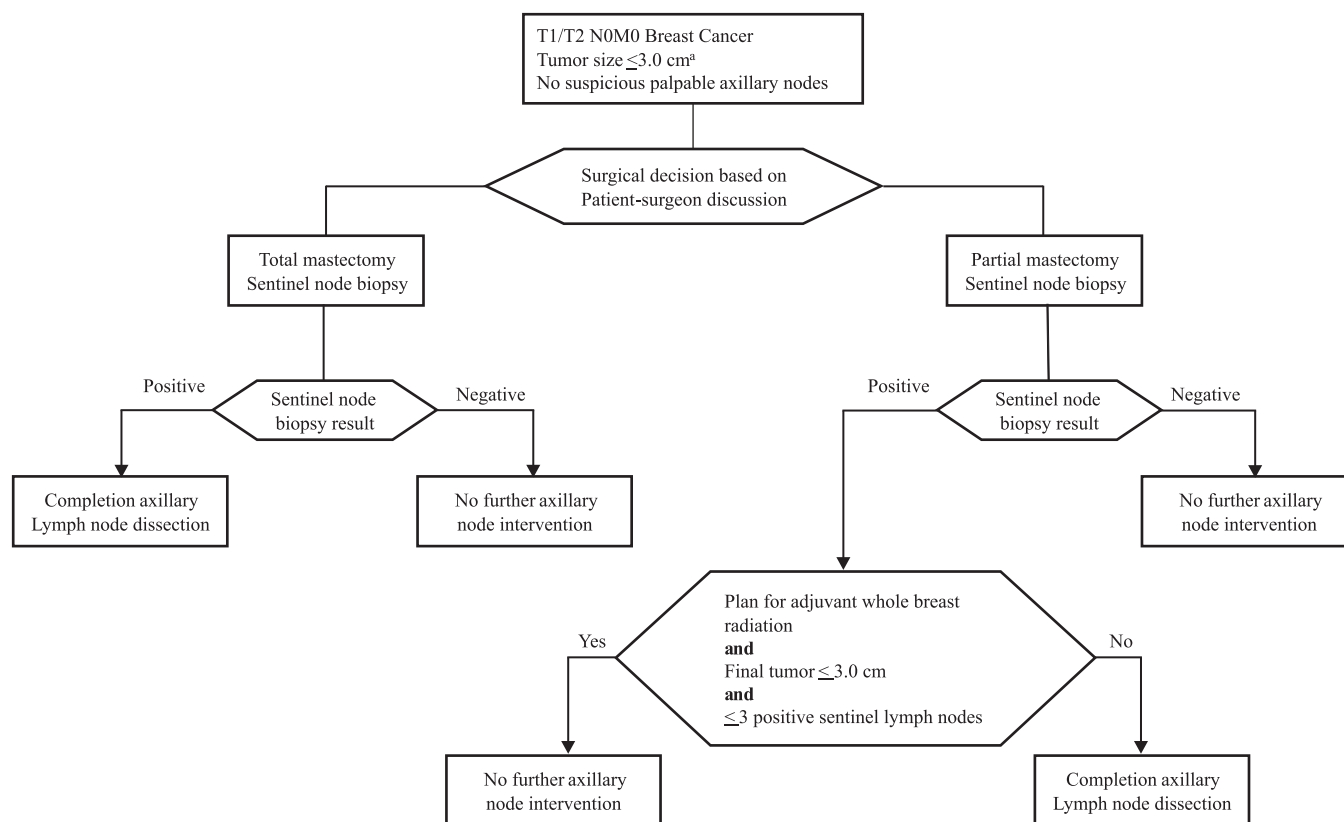


Fig 7: "If initial tumor size is > 3.0 cm or patient is to undergo neoadjuvant chemotherapy, algorithm does not apply

In the last decade the recommendation has been ALND for clinically positive axilla and SLNB for clinically negative axilla with ALNB only if SLN is positive. Preoperative evaluation of the axilla is useful to triage axillary surgery. The NCCN recommends US guided FNAC/ core biopsy of clinically positive axillary lymph node. If negative, then SLNB should be considered. If positive, then axillary dissection is recommended.

Z0011 & Beyond: The American College Of Surgeons Oncology Group (ACOSOG) published the results of Z0011⁴ study recently and the results have been practice changing. The trial recommends that a certain population with breast cancer with T1/T2 lesion undergoing breast conservation surgery and whole breast radiation with ER/PR tumors with one or two SLN positivity (low nodal burden) do not require further axillary dissection because there is no oncological difference. Secondly, intra operative assessment of SLNB has lost significance since the Z0011. But if Z0011 is put into practice then the big question is how to determine adjuvant systemic therapy

for patients eligible for Oncotype DX or MammaPrint? In conclusion, managing the axilla has to be tailored according to the individual tumor biology and genomic landscape.

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GUEST ARTICLE

HEREDITARY BREAST CANCERS: BENCH TO BEDSIDE

Cancer is a genetic disease i.e. abnormal change (mutations) in the genetic code results in uncontrolled growth and spread of the abnormal cells. Most of the cancer (90%) are caused by mutations that are acquired (Somatic Mutation) by various inciting factors, like personal habits, environmental/industrial exposure, certain infections, radiation etc. But sometimes, these mutations occurs in the germ cells (i.e. sperms or ova) and are passed down to the next generation (germline mutations) resulting in inheritable form of cancer called Hereditary Cancers (10%). Less than 10 percent of all breast cancers are associated with germline (inherited) genetic mutations. Majority of these hereditary breast cancers are associated with mutations in the 2 tumor suppressor genes: breast cancer type 1 and 2 susceptibility genes (BRCA1 and BRCA2) and less commonly, are related to mutations in the TP53, PTEN and CDH1 genes.

All breast cancers arise due to genetic aberrations and can be broadly classified in to the following three categories:

- Hereditary (5-10 %)
- Familial (15-20 %)
- Sporadic (70-75 %)

Hereditary breast cancer (HBC) is characterized by features such as early age of onset, greater incidence of bilateral breast cancer, greater incidence of multiple primary cancer such as cancer of the breast and ovary and an autosomal dominant inheritance pattern for cancer susceptibility. Hereditary breast cancers are associated with inherited highly penetrant genetic mutations.

Familial breast cancer does not have the characteristics of HBC as listed above but is associated with a family history of one or more first- or second-degree relatives with breast cancer. Familial breast cancer is more prevalent in people with unusually high cases of family members affected by cancers like breast cancer and ovary cancer. Mere coincidence is not expected to lead to a greater incidence of breast, ovarian or a related cancer in a particular family. In such cases there is very

high probability that genes have caused or contributed to its development.

Sporadic breast cancer is not associated with family history of breast carcinoma (through two generations including siblings, offsprings, parents, and both maternal and paternal aunts, uncles, and grandparents). High penetrant germline mutations do not play any role in these types of breast cancers. Sporadic breast cancers are a result of those accumulated mutations which were acquired by an individual during his/her lifetime and went undetected and uncorrected. They constitute the largest number of breast cancers.

Features of Hereditary Breast Cancer

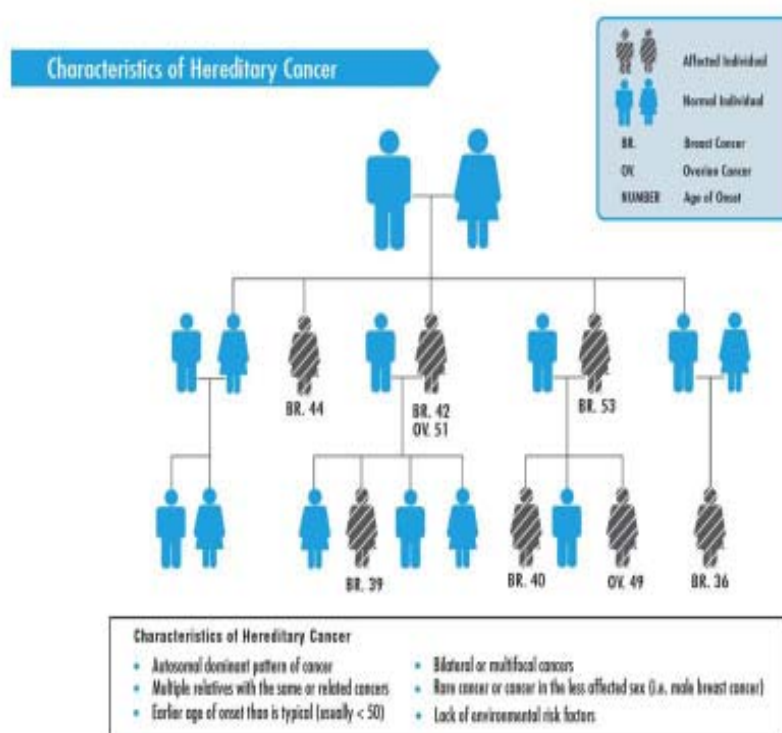
- Commonly show an autosomal dominant trait (offspring have a fifty percent chance of inheriting the mutation), and both a maternal or paternal inheritance pattern.
- Early age on onset of breast cancer (often before age 50).
- Increased incidence of other cancers like ovarian cancer, pancreatic cancer, melanoma etc.
- Susceptibility for multiple cancers and bilateral disease.
- Male breast cancer.

Genetic Variants for Hereditary Breast Cancer

Not all hereditary breast cancers and the generations/ individuals who are carrier of the particular genetic alteration exhibit the clinical symptoms. This variable exhibition of disease is described by a phenomenon called "Penetrance", defined as the proportion of individuals with a variant/mutation causing a particular disorder and exhibit clinical symptoms of that disorder. Genetic variants associated with cancer can be broadly classified in to the following three categories based upon their penetrance:

- High penetrance variants (Rare)
- Moderate penetrance variants (Rare)
- Low penetrance variants (Common)

High penetrance variants: These highly penetrant germline mutations are responsible for hereditary breast cancers and are rarely observed. These include high risk mutations in breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*) genes (Hereditary Breast and Ovarian Cancer Syndrome; HBOC). Risk of breast cancer is higher in *BRCA1* than in *BRCA2* mutation carriers. The risk of developing breast cancer by the age 70 years is 55% to 65% for *BRCA1* and



45% to 47% for BRCA2 mutation carriers. Other genes in which these high risk mutations can occur include *TP53* gene (Li-Fraumeni Syndrome), *PTEN* gene (Cowden syndrome) and *STK11* (Peutz-Jeghers syndrome).

Moderate penetrance variants: The penetrance of these mutations is lower than that of high penetrance mutations. Due to this, moderate penetrance variants pose a lower cancer risk compared to the high penetrance variants. Some of the genes in which these moderate penetrance variants occur include *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1* and *PALB2*. They pose a 2-4 fold increased risk for breast cancer. For example, the *CHEK2**1100delC variant results in an approximate two-fold increase of breast cancer risk in females.

Low penetrance variants: These types of variants (also called low-penetrance genes, alleles, and polymorphisms) are relatively common in the general population. They pose a 1.1-1.4 fold increased risk for breast cancer. As compared to the high and moderate penetrance mutations discussed earlier, these low penetrance polymorphisms pose minimal risk of developing cancer to an individual. But due to their common prevalence in general population, their overall contribution to cancer risk in a population is much greater than high risk mutations in BRCA1 and BRCA2.

Expressivity in Hereditary Breast Cancer

Individuals within the same family who carry the same mutation may have significantly different types of cancer and age of onset. This phenomenon is called expressivity. There is accumulating evidence that gene-gene interactions (eg, the position of the mutation in the BRCA1 or BRCA2 gene and genetic variation in other genes) and gene-environment interactions, including age, hormonal or reproductive factors, and lifestyle factors, account for this variability.

Hormonal risk-modifiers: Reproductive factors and oral contraceptive use have been analyzed to determine their influence on breast cancer risk in BRCA1 and BRCA2 mutation carriers. Menarche before age 12 and low parity have been associated with an increased risk for breast cancer. In BRCA2 mutation carriers, first childbirth at later ages was associated with an increased risk of breast cancer compared with first childbirth before age 20 years, whereas in BRCA1 mutation carriers, first childbirth at age 30 years or later was associated with a reduced risk of breast cancer (compared with first childbirth before age 20 years). Women with deleterious BRCA1 mutations who breast-fed for a cumulative total of more than one year had a statistically significantly reduced risk of breast cancer.

Genetics: Mutation location and genetic variation appear to impact BRCA1 and BRCA2 gene function and play a role in modifying BRCA-associated cancer risks. For example, mutations occurring within the central region of the BRCA2 gene, called the ovarian cancer cluster region, compared to mutations in the 5' or 3' region, may be associated with a significantly decreased risk of breast cancer, but a significantly higher risk of ovarian cancer in women and possibly a lower risk of prostate cancer in male carriers.

Cancer Genetic Counselling and Gene Testing

Women carriers of BRCA1 and BRCA2 mutations have a markedly high lifetime risk of breast cancer of 50 to 85 percent. Higher prevalence of BRCA 1 and BRCA 2 mutations is found among individuals with a personal history of breast cancer and/or a family history of breast and ovarian cancer, especially if associated with young age of onset, multiple tumors, and involvement of male family members affected with breast cancer. Pre-test cancer genetic counselling is required prior to gene testing.

Cancer Genetic Counselling is the process of making an individual understand and adapt to the medical, psychological and familial implications of genetic contributions to cancer.

It is a multi-step process involving:-

- Personalized cancer risk assessment
- Collection and interpretation of family histories
- Education about inheritance, cancer gene testing, treatment options and prevention options
- Counseling to promote informed medical choices and adaptation to the cancer risk

The cancer gene testing is typically recommended for the individuals diagnosed with a hereditary cancer (proband) or/and to the family members. Cancer gene testing is a DNA testing where detail analysis of a gene(s) is done to ascertain the changes in the genetic code (single point mutation/insertion/deletion/rearrangement etc). BRCA1 and BRCA2 are large genes, distributed over approximately 100,000 base pairs of genomic DNA. More than 500 types of mutations in BRCA1 and over 300 mutations in the BRCA2 gene have been reported in the literature. Deletions/duplications are rare as compared to point mutations. It becomes imperative, therefore to check for the complete gene to find any novel mutations. It is also good for testing the hot-spot mutations prevalent in a particular community. For

example the Ashkenazi Jews come from such a region where every 1 in 40 persons are carriers of 185delAG founder mutation in the exon 2 of the BRCA1 gene with increased risk for breast cancer. The other most common mutation is 5382insC in exon 20 of the BRCA1 gene and 6174delT in the BRCA2 gene. Individual mutation frequencies among Ashkenazi Jewish breast cancer patients are 6.7%, 2.2% and 4.5%, respectively. The mutation frequencies in the Indian population are not well studied so far. Gene testing information really makes a difference even if an individual is known to have a family history of cancer. Further, determination of abnormal gene involved and its related risk of developing certain cancers allows implementation of cancer specific risk-reducing interventions: better screening, surgical prevention, and chemoprevention. This information can be helpful for individuals as well as their family members in preventing cancer from developing.

Techniques for Gene Testing

Sequencing is the technique which allows us to look at the individual base pairs and detect point mutations. The two different types of sequencing reactions are Sanger sequencing also known as capillary electrophoresis and next-generation sequencing techniques (NGS) like pyrosequencing. The NGS systems differ from their conventional counterpart in terms of high throughput and more depth of genome coverage per run.

Management of Hereditary Breast Cancer

There is no single management strategy in reducing the risk of breast cancer for all women with genetic syndrome. The decision is individualized and is highly dependent upon the patient's own set of values, and the values may change over time, for example, pre- and post-child bearing. Women with hereditary breast and ovarian cancers (HBOC) syndrome have inherited mutations in breast cancer Type 1 and 2 susceptibility genes (BRCA1 and BRCA2) and markedly elevated risks of breast cancer and ovarian cancer. Men with HBOC syndrome have increased risk for breast and prostate cancer, while both men and women with HBOC syndrome have other cancer risks, such as increased risk of pancreatic cancer. Effective strategies for breast and ovarian cancer risk-reduction include cancer surveillance, risk-reducing surgery, and/or chemoprevention. Patients who have a deleterious mutation should be advised of management strategies,

including risk-reducing surgery, surveillance, and chemoprevention.

Surveillance

For women who have not undergone risk-reducing surgery, breast and/or ovarian cancer surveillance entails

- Monthly breast self-examination beginning at age 18
- Clinical breast examination two to four times annually beginning at age 25
- Annual mammography and breast magnetic resonance imaging (MRI) screening (commonly alternated every six months) beginning at age 25 or individualized based on the earliest age of onset in the family
- Twice yearly ovarian cancer screening with transvaginal ultrasound and serum CA-125 levels (preferably day 1 to 10 of menstrual cycle for premenopausal women) beginning at age 35 years, or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family

For men with HBOC syndrome (with BRCA1 and BRCA2 mutations), cancer surveillance includes

- Monthly breast self-examination
- Clinical breast examination semi-annually
- Baseline mammogram with annual mammography if gynecomastia or parenchymal/glandular breast density is seen at baseline
- Appropriate prostate cancer screening

For men and women : Individuals with BRCA1 or BRCA2 mutations should also have annual full body skin examinations.

Prophylactic Surgery

Risk-reducing mastectomy is a highly effective strategy for breast cancer risk reduction, decreasing the incidence of breast cancer by as much as 90 percent or more in patients at risk of hereditary breast cancer. It should be considered by women with a BRCA1 or BRCA2 mutation.

Risk-reducing salpingo-oophorectomy is highly effective in reducing ovarian and fallopian tube cancers in both BRCA1 and BRCA2 mutation carriers (by approximately 80 percent) and breast cancer in premenopausal women. This surgery is recommended to mutation carriers by age 35 to 40 or when childbearing is completed, or individualized based on age of onset of ovarian cancer in the family.

Chemoprevention

Women who do not opt for risk-reducing surgery may consider surveillance and chemoprevention with Tamoxifen, though this is a less effective alternative to prophylactic mastectomy. Oral contraceptive use in BRCA1 and BRCA2 mutation carriers appears to decrease the risk of ovarian cancer, but mutation carriers who have used oral contraceptives are still recommended to undergo risk reducing salpingo-oophorectomy when childbearing is completed.

Further Testing

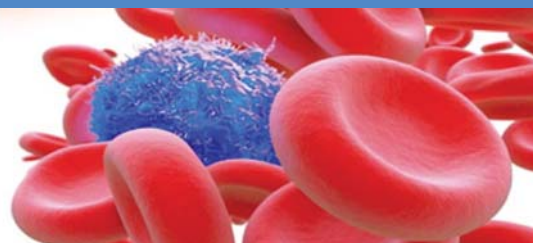
Patients with negative test results for a BRCA1 or BRCA2 mutation, however, with high risk for familial cancer should be offered further testing, as a genetic mutation may be present involving another gene MMR genes (Lynch Syndrome), STK11 gene (Peutz Jeghers Syndrome), PTEN (Cowden syndrome), p53 gene (Li-Fraumeni Syndrome) etc. Multi-gene panel testing may be recommended for such clinical situations.

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Yesterday's
Biopsy.....

Does not tell you about TODAY'S cancer

The Circulating tumor cells
(CTCs) do
(The Real Time Biopsy)



We enumerate CTCs for you

Centre for Molecular Diagnostics
& Cell Biology
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PERSPECTIVE

MICROSCOPE TO MICROARRAY: A MEDICAL ONCOLOGIST PURVIEW

Adjuvant chemotherapy, the difficult yet indispensable tool in cancer treatment substantially improves disease free and overall survival in all categories of breast cancers. Since its introduction in 1960s the adjuvant chemotherapy has seen a paradigm shift from a five drug combination regimen of cytotoxic agents, to the development and inclusion of taxanes in 1990s and more recently, the incorporation of eribulin into the management of metastatic breast cancer. However, with conventional treatment modalities, it also became evident that many patients relapse after treatment and many who qualified for established treatment protocols received no benefit from the treatment. An estimated three out of every four patients receiving this therapy would have survived without it.

Worldwide, Breast cancer is a major public health issue and is the leading cause of cancer mortality among women. It is estimated that over 522,000 women died due to breast cancer in 2012 of which more than 70,000 were from India alone. Breast cancer constitutes 22% of female cancer deaths in India. The pattern of breast cancer in India is very disturbing and the higher mortality is attributed to the non-availability of screening program. As a result, most of the breast cancer patients are detected at a more advanced stage. Breast cancer is a heterogeneous disease with early stage exhibiting small tumors, negative axillary nodes, successful treatment and a better prognosis. Whereas later stages present with a large tumor, positive axillary nodes and bad prognosis amenable for adjuvant chemotherapy. The screening and diagnosis of breast cancer patients at earlier stages benefits the patient, and also minimizes the financial burden. The three screening tests usually considered for early detection are self breast examination, clinical breast examination, and X-ray mammography.

Pathological examination has been the gold standard for diagnosis in breast cancer and its role has also included the elucidation of etiology, pathogenesis, clinicopathological correlation, and prognostication. The advent of newer technologies and the realization that breast cancer is heterogeneous has shifted the focus to prognostication, with increased attention being paid to

the identification of morphological features and immunohistochemical markers of prognostic relevance. The diagnosis of breast cancer is confirmed by a biopsy examination. Analysis of gross and microscopic morphological features performed on post-operative specimen and often the predicament of subsequent management of cancer also included factors such as tumor size, extent of involvement, presence of necrosis, and presence of metastasis or vascular invasion. The last five decades have seen a lot of transformation in the laboratory and clinical investigation and various molecular biomarkers have been identified. These biomarkers have shown great promise in augmenting the standard methods of assessing the disease status and in determining the best treatment option for breast cancer patients. The introduction of less invasive techniques to obtain smaller specimens of the diseased tissue for examination and the improvement in the microscopic techniques refined the prediction of tumor behavior which itself became strongly focused on microscopic features.

The traditional clinical approach to treat in situ and invasive breast cancer involves a combination of existing surgical, chemical and radiation based therapies. The decision as to whether to have further chemotherapy- which can cause considerable distress and side effects such as nausea and vomiting, fatigue and hair loss- can be a difficult one. In general, chemotherapy damages cells that are dividing, so the parts of the body where normal cells divide frequently are likely to be affected by chemotherapy. The mouth, intestines, skin, hair, bone marrow (the spongy material that fills the bones and produces new blood cells) are commonly affected by chemotherapy. Most therapies which are administered to treat breast cancer are quite toxic so it is better to select and use suitable therapy for the appropriate women. Some side effects of chemotherapy are serious medical conditions that need to be treated. The limitations of chemotherapy, especially the narrow therapeutic index and the lack of discrimination for cancerous and non cancerous cells have prompted the search for a greater target-directed approach to cancer treatment. Long-term side effects of chemotherapy could include damage to the heart, kidneys, lungs, nerves or reproductive organs. There is also a chance of developing a second cancer as a result of chemotherapy.

Prognostic and Predictive Biomarkers

The biology of each tumor is different and not all patients need to go through the difficult and challenging

chemotherapy after a surgical procedure to kill chances of cancerous cells recurring. The likelihood of the cancer returning is based on several factors, including the size and “grade” of the tumor, and whether it has spread locally to the lymph nodes. In addition to patient preferences and comorbidities, the clinical management of early stage and potentially curable breast cancer includes the use of several different clinical and molecular characteristics of the tumor to formulate therapeutic recommendations. The immunohistochemical 4 (IHC4) score is a pathological prognostic score that is a quantitative measurement of estrogen and progesterone receptor status, the her2 status and the Ki-67 score. The role of the IHC4 score in predicting local recurrence is evolving.

ER and PR

The presence of receptors of estrogen and/or progesterone hormone is currently an intrinsic part of routine evaluation in breast cancer patients. Hormone receptor status is typically assessed in the labs by performing immuno-histochemical staining (IHC) on tissue sections. This involves use of antibodies to stain the tissue sections for tumor antigens of interest and can be performed on both fresh-frozen and formalin-fixed paraffin-embedded (FFPE) tissue. Unfortunately due to lack of automation, the process of evaluating positivity of ER/PR staining is performed subjectively by a pathologist, thereby introducing variability in interpretation. The ER/PR status has been shown to have a significant predictive value on tumor response to hormonal therapy in both the metastatic as well as for adjuvant therapy after local excision but their prognostic value is still a case of debate.

HER2/neu

HER2/neu is an important transmembrane protein and a member of epidermal growth factor receptor family. It is a major prognostic marker that is currently a component of routine evaluation of primary invasive breast cancer. Currently HER2 protein is evaluated by IHC and its gene expression is determined using Fluorescent in-situ hybridization (FISH). Similar to the ER/PR results, the IHC and FISH results of HER2 are subjective and there is a factor of variability in interpretation. To augment the potential of HER2, an assay which measures the HER2 protein and functional HER2 homodimer levels on the cell surface in an FFPE section was developed. Preliminary findings suggest that measurement of activated form of HER2 has a prognostic value in the disease, however additional studies are

required to confirm these findings. HER2 has been shown to be a poor prognostic marker and its overexpression has been associated with worse overall survival.

Ki-67

The proliferation marker Ki-67 is one of the most controversially discussed parameters for treatment decisions in breast cancer patients. The most prevalent analysis method of Ki-67 antigen is the immunohistochemical evaluation. Patients with tumors that had a high-Ki-67-labeling index ($Ki-67 > 25\%$) had both worse DFS and OS than patients with tumors that had low-Ki-67-labeling index ($Ki-67 < 25\%$). ER status has been largely identified as being inversely correlated with Ki-67, with the higher rates of ER positivity shown in the lowest proliferating tumors. Moreover, it could be demonstrated that high levels of Ki-67 are associated with HER2/-neu positivity. However, to date no standard operating procedure (SOP) or generally accepted cut-off definition for Ki-67 exists. For this reason, both the interlaboratory and the interstudy comparability of Ki-67 are limited.

Despite all these advancements in the field of breast cancer, the strongest predictors for metastasis fail to classify accurately breast tumors according to their clinical behavior. Age, tumor size and Ki67 expression represent continuous variables whereas histologic grade and nodal status are ordinal variables. The ER and PR expression are variables with a bimodal distribution whereas HER2 gene amplification results are binary variables. When multiple factors measured with variable accuracy are associated with an outcome, the most accurate predictions can only be achieved by multivariate prediction models. This gave birth to multivariate prognostic models such as AdjuvantOnline and multigene predictors. Multigene prognostic assays are now endorsed by the American Society of Clinical Oncology, St. Gallen and National Comprehensive Cancer Network guidelines. Multigene assays provide credible information that could assist in decision-making process, facilitate treatment selection, and ultimately improve patient outcomes.

Multigene assays

In the last years, several multigene tests of risk assessment in early breast cancer have been developed to optimize the treatment and avoid unnecessary chemotherapy. These tests evaluate the genes which are involved in critical molecular pathways involved in the breast cancer metastatic cascade and are able to analyze molecular

subtypes of the cancer, risk of recurrence of early stage cancer, thereby enabling medical oncologists in identifying the benefit of chemotherapy in addition to the endocrine treatment in node-negative early breast cancer.

Three genomic assays are currently in use for breast cancer: Oncotype DX, MammaPrint, , PAM 50. While all three tests are somewhat similar, there are differences:

- The Oncotype DX test is used to estimate a woman's risk of recurrence of early-stage, hormone-receptor-positive breast cancer, as well as how likely she is to benefit from chemotherapy after breast cancer surgery. The assay uses RT-PCR technology using FFPE tissue block. The Oncotype DX test also is used to estimate a woman's recurrence risk of DCIS (ductal carcinoma in situ) and/or the risk of a new invasive cancer developing in the same breast, as well as how likely she is to benefit from radiation therapy after DCIS surgery. The Oncotype DX test analyzes the activity of 21 genes and then calculates and categorizes patients into Low, Intermediate, High risk based on a recurrence score number between 0 and 100; the higher the score, the greater the risk of recurrence.
- The MammaPrint test is used to estimate a women's recurrence risk for early-stage breast cancer. The 70 gene signature is shown to have independent prognostic values over clinical-pathological risk assessment in breast cancer patients. The assay is performed using a 25K microarray on a FFPE tissue block and is used for Early stage breast cancer (stage I and II), irrespective of ER, PR and HER2 status. The assay has also been validated on patients who have upto 3 positive lymph nodes. The RNA extracted from the tissue section is hybridized to a customized microarray which then calculates either a high-risk or a low-risk recurrence score.
- PAM50: The Prosigna Breast Cancer Prognostic Gene Signature Assay, made by NanoString, is a genomic test that analyzes the expression profiles for 50 genes and classifies tumors into four intrinsic subtypes (luminal A, luminal B, HER2-enriched, and basal-like). PAM50 test, designed to determine a risk of recurrence (ROR) score for patients with breast cancer, adds significant prognostic information to clinical decision. The assay is indicated for postmenopausal women with breast cancer whose tumors are stage I/II node-negative or stage II node-positive (1 to 3 positive nodes) and hormone receptor-positive. The test would be administered after patients have undergone surgery as part of locoregional standard-of-care. An algorithm is then used to combine the gene signature, intrinsic subtype, tumor size, and proliferation score.

- Over the time, it has become apparent that breast cancer is not a single type of tumor, but a group of different diseases with distinct molecular properties. Each of these molecularly different breast cancer types tends to respond differently (or not at all) to the various kinds of available therapy. As discussed previously ER/PR and HER2 status are subjective to pathologist's evaluation, hence a great need exists for better molecular characterization of tumor tissue. Determining the functional molecular subtyping based on the quantitative RNA expression of genes involved in the downstream pathways of ER, PR, HER2, and Ki-67 will enable us to accurately characterize the tumors based on the functional pathways which are involved in the growth of tumor. This would provide additional information about the tumor biology and help to facilitate the appropriate treatment selection.

Likewise microRNAs demonstrates a potential biomarker as these have been shown to be consistently upregulated and downregulated and have been shown to possess predictive and prognostic values. Many of these microRNAs have been linked to the currently used biomarkers in breast cancer management. But there are multiple concerns as far as microRNAs are concerned. The most important being the issue of normalization of the micorRNAs, and the problem of reproducibility of these results across different labs.

No doubt that the quantification of ER, PR and HER2 are being increasingly standardized and inter-laboratory reproducibility has improved substantially over the past few years. However, multigene signatures introduced an important concept into the need for multivariate prediction models. The introduction of molecular techniques such as CGH arrays, proteomics profiling and sequencing technology and the development of other high throughput technologies has opened up new avenues of exploration into the genesis of breast cancer. More importantly it has led to the realization that there are potentially new and specifically tailored avenues of treatment. Pathologists continue to play their traditional role in diagnosis but, as purveyors of the excised tissue, they now have the additional role of identifying biomarkers responsive to therapeutic manipulation, thus playing an inextricable role as diagnostic oncologists in the management of breast cancer. Such developments have defined a new role for the pathologist paving the Way for Personalized Medicine in a New Era.

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INFOCUS

NEXT-GENERATION-SEQUENCING FOR PERSONALIZED MEDICINE IN BREAST CANCER

The oldest reference to a growth anomaly like ‘cancer’, even though the term per se was not used, dates back to 3000 BC. An ancient Egyptian medical textbook called the Edwin Smith Papyrus, the oldest known surgical treatise, it describes 8 cases of tumors or ulcers of the breast that were removed by cauterization. The writing concluded that “There is no treatment” for such growth anomalies. The term cancer has its origin in the times of the Greek physician Hippocrates (460-370 BC). He used the terms *carcinos* and *carcinoma* to describe non-ulcer forming and ulcer-forming tumors. In Greek, these words refer to a crab and were probably used in view of the phenotypic expression of the disease that is the finger-like spreading projections from a cancer resembling the shape of a crab (1). Celsus (28-50 BC), a Roman physician, translated the Greek terms, *carcinos* and *carcinoma*, into the Latin word for crab, cancer. Galen (130-200 AD), another Greek physician, used the word *oncos* (Greek for swelling) to describe tumors. Although the crab analogy of Hippocrates and Celsus is still used to describe malignant tumors, Galen’s term is now used as a part of the name for cancer specialists-oncologists (2).

Cancer of breast is the leading cause of death in women, with almost 1,300,000 cases reported and 465,000 deaths worldwide in 2011 (3). It is one of the more complex cancer characterized by several clinical, pathological and prognostic sub-groups, reason being the large range of genetic alterations. In the past few decades, intensive research and adoption of sophisticated, high-throughput technologies have shed insight into this molecular complexity but the knowledge is still poorly utilized to the advantage of the cancer patients. Detection and identification of patients who are likely to respond to treatment so as to avoid unnecessary toxicity are the critical issues that need to be addressed through a comprehensive and systematic approach. The translation of this knowledge database into clinical benefit is the requirement of the moment.

The National Health Institute and the US Food and Drug Administration (FDA) defines personalized medicine as “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease” (accessed January 3rd, 2013) and as the best way to obtain “the best medical outcomes by choosing treatments that work well in a given person according to its genomic profile, or with certain characteristics in blood or cell surface proteins” (4).

Traditionally, parameters such as patient’s age, pathological tumor size, axillary lymph node involvement, tumor grade, immunohistochemistry (IHC) based expression pattern of hormone receptor (estrogen receptor, ER and progesterone receptor, PR) and HER2, ERBB2 (gene for HER2) amplification (FISH based) have been used to treat breast cancer patients (5). Challenges and limitations with IHC such as difficulty in standardization, reproducibility, oversight of mutation based protein activity alteration etc. have pushed the researchers to develop alternative methods. Efforts in the last decade have given way to tests involving quantitative measurement of gene expression based on DNA microarrays or quantitative RT-PCR, multi-gene expression signatures, gene sequencing etc. (6, 7, 8, 9).

The multi-gene signatures offer both prognostic and predictive value, which has been validated by various meta-analyses and the MAQC (Microarray Quality Control) consortium (10, 11).

The Mamma Print assay is a 70-gene test useful for both node negative and positive breast cancer patients and for post-menopausal women (12, 13, 14, 15) and stratifies patients into a high-risk or low-risk category. It is beneficial for predicting distant recurrence/metastasis post-surgery, response to neo-adjuvant and adjuvant chemotherapy (16, 17). The technical limitation of the test is that it requires a large amount of fresh tumor sample and is useful for patients younger than 61 years with a lymph node-negative tumor measuring less than 5 mm³.

The Oncotype DX assay is a 21-gene expression based test for non-invasive ductal carcinoma and invasive carcinoma. Based on qRT-PCR, the test gives a recurrence score that stratifies patients into three groups according to their 10-year risk of relapse and has been validated in a cohort that included tamoxifen-treated, ER+, lymph node negative patients (18, 19). The score also predicts benefit from neo-adjuvant and adjuvant chemotherapy (20, 21, 22).

Although, the aforementioned expression-based approach has value for recurrence prediction and benefit from neo-adjuvant/adjuvant chemotherapy, it has various limitations, such as oversight of clinical behavior of the tumor depending on the mutation pattern, which are overcome to a large extent by deep sequencing of tumors. Next generation sequencing (NGS) based comprehensive analysis of mutational landscape of the tumor aid in identification of clinically significant mutations, and expands the therapeutic possibilities available to the breast cancer patients. Moreover unlike, Oncotype DX and MammoPrint assay, NGS based test can be used for all types of breast cancer patients independent of their hormone-receptor status, HER2 status, lymph node status and prior treatment history.

Next Generation Sequencing (NGS) Based Testing

At its onset, NGS based personalized medicine in cancer consisted of genetic testing for mutations in a single gene, typically known as the 'driver' mutation in a gene. This was followed by treatment with targeted therapies against the driver gene or the pathway activated. Such a treatment regimen provided more effective and less toxic treatment options over conventional chemotherapy and radiotherapy. However, the redundancy and multi-layer control of pathways in cancer cells underlay the lack of response in certain individuals positive for 'driver' mutations, making it necessary for a deeper look at the genetic makeup of the tumors. For example, anti-HER2 drugs, Herceptin (trastuzumab) and Tykerb (lapatinib) are approved for the treatment of HER2-positive breast cancer (23). Poor response to drugs such as these can occur as a result of mutations in other genes like as *PIK3CA* and *EGFR* (24). This dictates a transition from a single-gene test approach to a NGS based multi-gene test like the Strand Somatic 48 gene test. Hence, NGS based multi-gene testing helps identify a large landscape of mutations, thus ensuring minimal loss of time before arriving at an effective therapy option.

Reclassification of Cancers Using Tumor Mutation Profiles

Based on IHC results, breast cancer patients are commonly categorized as HER2-negative or HER2-positive and therapy regimens are rolled out; but the picture is not as simple. Occasionally driver genes, such as *ERBB2*, even though not detected as over-expressed by IHC, might harbor activating mutations and thus, still drive cancer growth. Such tumours would be amenable to anti-HER2 therapy. Identification of such novel driver

mutations thus, is essential in the attempt to personalize cancer therapy (25).

Shared Tumor Mutations Across Different Types of Cancer Tissues

Comprehensive genomic profiling of cancers has resulted in identification of frequently disrupted pathways in the various cancer types. For example, in glioblastomas, p53, RB1 and receptor tyrosine kinases are the three most frequently disrupted pathways (26), whereas in estrogen receptor positive breast cancer, somatic mutations often affect pathways such as p53/RB, PI3K/AKT/mammalian target of rapamycin, and mitogen-activated protein kinase (27). The 48-gene panel incorporates genes from multiple pathways into a single panel, and is thus comprehensive. Moreover, tumors of different origins can have the same driver mutations and hence, drug approved for a driver mutation in a specific cancer might show benefit in another cancer type with the same driver mutation. This supports the idea of testing a tumor for mutations and genes other than the ones typically associated with that tumor. For example, trastuzumab, anti-HER2 drug, was initially tested and approved for HER2 amplified breast cancer (28, 29). Later, identification of HER2 amplification in gastric cancer led to the successful introduction of trastuzumab therapy in this tissue type as well (30, 31). In the light of such observations, multi-gene panel provides insight into potential treatment options inferred from other tumor types.

Strand Somatic 48-Gene Test

The Strand Somatic 48-Gene Test utilizes the Illumina TruSeq Amplicon cancer panel targeting mutational hotspot regions in 48-genes. The DNA extracted from formalin-fixed, paraffin-embedded tumor samples from cancer patients is sequenced on a MiSeq sequencer. Genomic alteration data obtained is analyzed using Strand NGS and interpreted for clinical relevance using StrandOmics, both proprietary NGS analysis platform and the clinical interpretation and reporting platform respectively. Figure 1 depicts the genes and pathways covered by the 48-gene panel.

Strand Advantage Tissue Specific Panel (TSP) for Breast Cancer

Strand Advantage TSP for breast cancer is a sub-set of the Strand Somatic 48-Gene test, tailored to assist breast cancer patients, to be performed preferably before beginning first line of therapy. This test is aimed at identifying those mutations that can impact standard of

ABL1	AKT1	ALK	APC	ATM	BRAF	CDH1	CDKN2A
CSF1R	CTNNB1	EGFR	ERBB2	ERBB4	FBXW7	FGFR1	FGFR2
FGFR3	FLT3	GNA11	GNAQ	GNAS	HNF1A	HRAS	IDH1
JAK2	JAK3	KDR	KIT	KRAS	MET	MLH1	MPL
NOTCH1	NPM1	NRAS	PDGFRA	PIK3A	PTEN	PTPN11	RBI
RET	SMAD4	SMARCB1	SMO	SRC	STK11	TP53	VHL

Pathways in cancer	Genes involved	Pathways in cancer	Genes involved
MAPK signalling	Survival Pathways AKT1, BRAF, HRAS, KRAS, NRAS, PIK3CA, PTEN, PTPN11, SRC	Apoptosis pathway	RB1, TP53
PI3k signalling	AKT1, PIK3CA, PTEN, STK11, HNF1A	Cell cycle / pRb pathway	CDKN2A, RB1, SMAD4, TP53
Receptor Tyrosine Kinase	ABL1, AKL, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, FLT3, KDR, KIT, MET, PDGFRA, RET	DNA damage response and repair pathway	ATM, MLH1, RB1, TP53
Angiogenesis signalling	VHL	Hedgehog signalling pathway	SMO
Notch signalling	FBXW7, NOTCH1	Cell metabolism	IDH1
Wnt signalling	APC, CTNNB1, SMAD4	Adherens junction pathway	CDH1, CTNNB1, SRC
Cytokine signalling	CSF1R, JAK2, JAK3, PTPN11		
GPCR signalling	GNA11, GNAQ, GNAS, HRAS, JAK3, KRAS, PIK3CA, SMO		

Figure 1: Strand Somatic 48-Gene Panel

care therapy. The test profiles and specifically analyzes six genes namely, *ERBB2*, *EGFR*, *PTEN*, *PIK3CA*, *SMAD4*, and *VHL*. The test is predictive of response or poor response to chemotherapy and targeted therapy. Few breast cancer TSP test based drug-gene associations are enlisted below:

- Trastuzumab, Pertuzumab, Lapatinib: Though anti-HER2 therapy is approved for HER2-positive breast cancer patients, activating mutations in either *PIK3CA* or *EGFR* gene may indicate poor response to the therapy (32, 33). Moreover, activating mutation in *ERBB2* (HER2) is indicative of benefit from anti-HER2 therapy, even if the patient is HER2-negative.
- Everolimus: Approved for hormone receptor-positive, HER2-negative breast cancer patients, in combination with exemestane. Mutations in *PIK3CA* or loss of *PTEN* indicate possible response to everolimus (34, 35).
- Bevacizumab: Mutations in *VHL* indicate possible response to bevacizumab therapy (36).
- Tamoxifen: Though approved for hormone receptor-positive breast cancer patients, presence of an activating mutation in *EGFR* gene indicates poor response to tamoxifen (37).
- 5-fluorouracil: Presence of a loss of function mutation in *SMAD4* gene indicates possible response to 5-fluorouracil therapy (38).

The therapeutic window can be further expanded by opting to analyze the complete set of 48 genes (Strand Advantage extended TSP, also known as Strand Somatic 48-Gene test), thus taking into consideration potentially beneficial off-label drugs. About 500 somatic cancer samples have been analyzed by us till date. In the case of 116 breast cancer cases, clinical utility, i.e. response or lack of benefit information, was reported in 64 % of the cases. To cite an example, a female patient diagnosed with invasive ductal carcinoma of left breast (Stage IIIC HR-negative, HER2-positive) was found to harbour an activating mutation in *PIK3CA* gene. Mutation in *PIK3CA* indicates possible response to mTOR inhibitor, such as everolimus, and poor response to anti-HER2 therapy such as trastuzumab.

To conclude, advances in treatment strategies, till date, have not been accompanied by a parallel improvement in the survival rates. The Strand Somatic 48-Gene test based molecular profiling and interpretation gives insight into patient responsiveness to approved treatment, potential treatment regimen inferred from other tumor types and patient prognosis. Treatment regimens aided by such an approach are likely to translate into more effective and cost-effective care.

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BREAST COSMESIS

CHALLENGES IN BREAST IRRADIATION AFTER ONCOPLASTIC SURGERY FOR EARLY BREAST CANCER

With the incidence of breast carcinoma reaching epidemic proportions in the younger population, it is an onus on the treating oncologists to achieve good cosmesis in addition to good local control.

Surgical oncologists worldwide have moved away from psychologically devastating mastectomies to more acceptable oncoplastic surgeries for early breast cancer. However, in order to achieve a comparable disease free and overall survival as after mastectomy, breast conserving surgery needs to be followed up with whole breast irradiation. And here the radiation oncologist joins hands with the surgeon in providing a good to excellent cosmetic outcome by judicious use of radiation techniques, doses and fractionation schedules.

Breast cosmesis is assessed on parameters such as skin discoloration, redness, fibrosis and nipple retraction. The degree of cosmesis is based on how similar the treated and the untreated breasts appear. Cosmesis depends on patient related and treatment related factors.

Patient related factors leading to fair to poor cosmesis include presence of comorbidities that may delay tissue

healing such as diabetes and hypertension, large or very small size of the breast and presence of connective tissue disorders. Of these, breast size can be taken care of by augmentation or reduction surgery in the affected breast followed by irradiation.

Treatment related factors include large irradiation volumes, energy of the beam, high dose per fraction and technique of lumpectomy boost and interaction of chemotherapy with radiation in addition to extent of surgical excision and oncoplastic expertise. Irradiation volumes need to be planned wisely based on established guidelines to include the axilla or not.

Cobalt therapy units in which there was a considerable build up of dose under the skin leading to fair to poor cosmesis, have given way to megavoltage linear accelerators. Megavoltage beams of 6 MV with wedges gives a good homogeneous dose distribution within the breast tissue and a skin sparing effect. Higher beam energies may be used for larger separations.

Radiation to the whole breast has evolved from two-dimensional wedged technique to three-dimensional planning (volume based), which allows better sparing of the underlying organs at risk such as ipsilateral lung and heart.

Development of Intensity Modulated Radiotherapy (IMRT) with or without image guidance and respiratory gating revolutionized radiation delivery in this scenario. High definition multileaf collimators allow a homogenous



Fig 1 Patient with cast on CT simulator

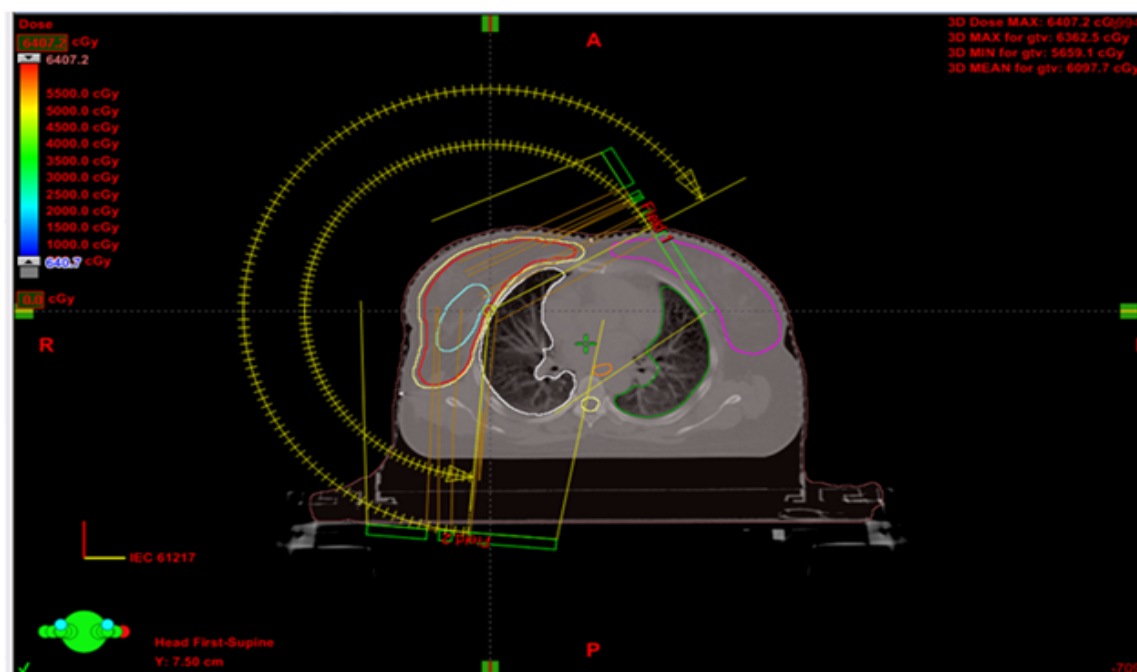


Fig 2 VMAT radiotherapy plan using two semiarcs for a patient undergoing adjuvant radiotherapy following BCS

dose distribution to the entire breast. Further, introduction of volumetric arc therapy (VMAT) has shortened the treatment delivery time per session considerably, achieving better patient compliance. It is a form IMRT wherein, there is continuous delivery of radiation along with gantry rotation around the patient and change in dose rate of the incident beam. Filter free beams can be used to further increase the dose rate.

One major limitation in this entire cycle of surgery followed by chemotherapy and followed by radiotherapy

has been the prolonged course of radiotherapy extending over a period of five to six weeks. In order to overcome this problem, shorter schedules of radiotherapy with higher dose per fraction have been validated in major clinical trials and are being used worldwide to improve patient compliance and better utilization of radiotherapy resources. It has now been incorporated in the NCCN guidelines as well. However, hypofractionation should be avoided in large breast volumes as it may hamper long term cosmetic outcome.

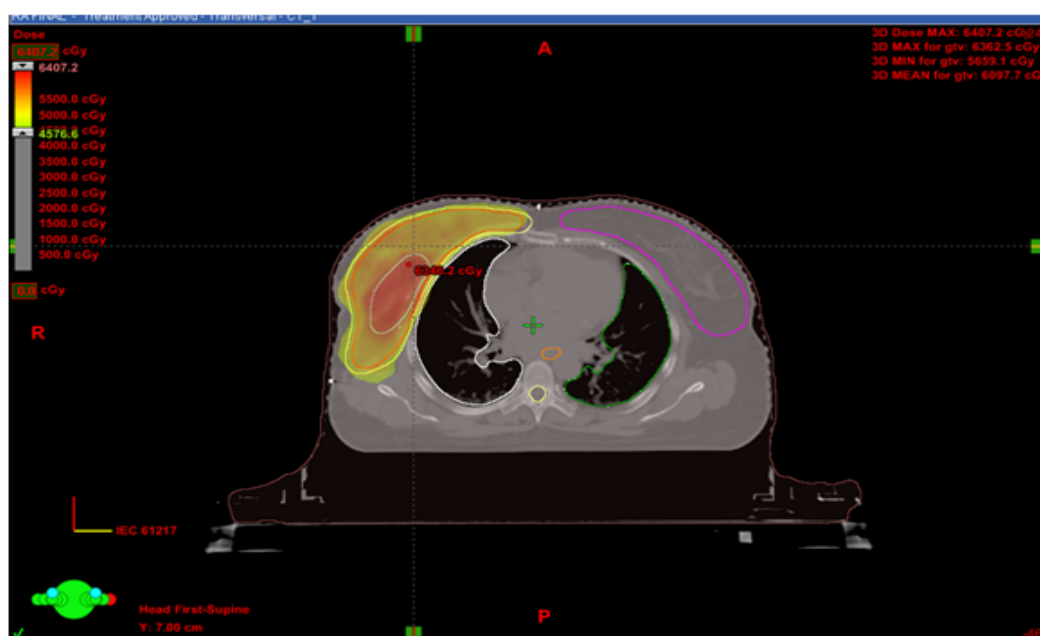


Fig 3 Dose color wash showing adequate dose coverage to the target volumes and sharp dose gradient leading to sparing of the underlying lung.



Fig 4 Patient on the Linear Accelerator couch in treatment position with the Orfit cast on for immobilisation and reproducible set up

In an attempt to further shorten this duration, the concept of accelerated partial breast irradiation (APBI) has taken ground in a much selected group of patients. It has been observed that only 3-4% of ipsilateral breast tumor recurrences occur outside the original tumor bed. Therefore, highly focused radiation to the tumor bed with a 1-2 cm margin can be given with high dose per fraction. In addition to shorter treatment time, this can also achieve better cosmesis by considerably reducing the planning target volume (PTV). It has been repeatedly shown that large breast volumes (resulting in larger PTVs) adversely affect the cosmetic outcome. However, of the various techniques available for APBI including interstitial brachytherapy (IBT), mammosite, electron or kilovoltage photon therapy and 3-D conformal radiotherapy, IBT has given the best oncological and cosmetic outcome so far with the longest follow up period.

There are various techniques of delivering a sequential boost to the lumpectomy cavity in high risk patients (age less than 50 years and Grade III) including interstitial brachytherapy, en face electron beam and tangential photon beams. Proper selection of the technique has to be done depending upon the location and depth of the cavity, to achieve adequate dose and reasonable cosmesis. Boost can also be given with Simultaneous Integrated Boost (SIB IMRT) technique which not only shortens the treatment duration to five and a half weeks, but also achieves an excellent cosmesis.

As an increasing number of patients are opting for breast conserving surgery, we at the Department of Radiation Oncology, RGCI, are striving to achieve an excellent to good cosmesis with static IMRT or VMAT technique.

An orfit cast (4 or 6-clip) is made for patient immobilisation. A simulation CT scan with 5 mm slices is acquired in the treatment position. Ipsilateral breast tissue, axilla and organs at risk (namely ipsilateral lung, heart, spinal cord, oesophagus and opposite breast) are contoured on each slice with the help of radiopaque markers placed on the patient's body at the time of simulation. The lumpectomy cavity is delineated with the help of seroma and surgical clips. The planning target volume is carefully contoured especially in the axillary and inframammary region where wet desquamation during radiation may hamper long term cosmesis. Fractionation schedule for the entire breast and axilla is kept at 1.8 Gy per fraction. Lumpectomy cavity boost is given by SIB IMRT. While evaluating the radiation plan, special attention is paid to the dose to skin of the ipsilateral breast, which should not exceed 45 Gy. Also a homogenous dose distribution throughout the breast tissue is mandatory for good cosmesis. The patient is kept on weekly follow-up during radiotherapy and closely watched for radiation dermatitis. This schedule is well tolerated with nearly 95% of the patients achieving excellent to good long term cosmesis.

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