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Focus Area:
BREAST CANCER



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From the Desk of Director Research

Breast cancer is the most common cancer in women worldwide. It is also the principal cause of death from cancer among women globally. Despite the high incidence rates, in Western countries, 89% of women diagnosed with breast cancer are still alive 5 years after their diagnosis. Screening programs, better treatments and a general increase in awareness have resulted in death rates declining from breast cancer over the past two decades. There is geographic variation, with the standardized age incidence rate being lower in developing countries than industrialized countries. The chance of developing invasive breast cancer at some time in a woman's life is approximately 1 in 8, and the chance that breast cancer will be responsible for a woman's death is about 1 in 35.

Carcinoma of the breast consists of a heterogeneous group of lesions; most are adenocarcinomas. Infiltrating ductal carcinoma undoubtedly is the most common histologic type of invasive breast cancer, comprising approximately 75% of all tumors and best treated using a multidisciplinary approach, combining the efforts of surgery, radiation therapy, and systemic treatments. Understanding the indications and contraindications for each of these modalities will provide the practicing surgeon the most up-to-date algorithms for the management of his/her patient.

Breast cancer is a complex, molecular disease, in which a number of cellular pathways involving cell growth and proliferation, such as the MAPK, RB/E2F, P13K/AKT/mTOR, and TP53 are altered. These pathways represent molecular mechanisms that orchestrated by various genes. Although the nature of breast cancer is complex and has frustrated previous attempts at treatment or prevention, the elucidation of its molecular nature over the last several decades is now providing targets for effective therapies to treat the disease and hopefully one day to prevent it.

About 5% to 10% of breast cancers are thought to be hereditary, caused by abnormal genes passed from parent to child. Most inherited cases of breast cancer are associated with two abnormal genes: BRCA1 (Breast Cancer gene one) and BRCA2 (Breast Cancer gene two). Everyone has BRCA1 and BRCA2 genes. The function of the BRCA genes is to repair cell damage and keep breast, ovarian, and other cells growing normally. But when these genes contain abnormalities or mutations that are passed from generation to generation, the genes don't function normally and breast, ovarian, and other cancer risk increases.

Breast cancer is striking young population and achieving good cosmesis from reconstruction is essential. Our Guest Author Dr. Anotnio Toesca, European Institute of Oncology, Milan, Italy has elaborated on this in the article entitled "Robotic Nipple Sparing Mastectomy: Current Perspective and State of the Art Techniques".

The present issue of the Cancer News highlights the newer advances in the field of breast cancer and features the regular articles, such as Guest Article, Outlook and In Focus. We are grateful to Dr Antonio Toesca, Dr Paolo Veronesi, Dr Virgilio Sacchini, Dr Andrea Manconi, Dr Nickolas Peradze, Division of Breast Surgery, European Institute of Oncology, Milan, Italy for the "Guest Article" and Dr Amit Verma, Consultant Molecular Oncology and Cancer Genetics, Max Cancer Center, New Delhi.

Dr Anurag Mehta

CONTENTS

- **Guest Article:** Robotic Nipple-Sparing Mastectomy: Current Perspectives and State of the Art Techniques [3-6]
- **Cancer Control:** Grilled or Smoked Meats, Even Fish, Can be Risky, Social Ties and Higher Survival [6]
- **Outlook:** Hereditary Breast Cancers [7-10]
- **New Technologies:** Mutation Analysis of Cell-Free DNA & Single CTC, Saliva as an Alternative Specimen Source for NGS [10]
- **Perspective:** Hypofractionation in Carcinoma Breast [11-13]
- **In Focus:** Oncoplastic Breast Cancer Surgery: An Overview [14-16]
- **Globe Scan:** Microsurgical Breast Reconstruction, Breast Cancer in Cameroon [16]
- **Abstracts of RGCIRC [18]**
- **Appeal for Funding Research [19]**

Research & Analysis Team
Research Department

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GUEST ARTICLE**ROBOTIC NIPPLE-SPARING MASTECTOMY: CURRENT PERSPECTIVES AND STATE OF THE ART TECHNIQUES****Introduction**

The application of robotic technology in various specialties has exerted a significant impact on surgical techniques and on the postoperative outcome of patients over the past decade. Robotic surgery is today considered a valid option for radical prostatectomy, radical cystectomy, colorectal surgery and hysterectomy, with the majority of cases being dedicated to oncologic procedures [1]. Despite the lack of a natural cavity needed for endoscopic viewing, applications of robotic surgery have also recently emerged for superficial organs, such as in the fields of thyroidectomy [2], oropharyngeal surgery [3], and plastic and reconstructive surgery [4].

Technical innovations have made it feasible to conduct endoscopic nipple-sparing mastectomy which has been reportedly well-tolerated, safe, and associated with greater patient satisfaction [5]. Furthermore, several clinical trials have now been conducted to provide follow-up data regarding the oncological success of endoscopic breast surgery [5]. However, the manual control of a two-dimensional endoscopic in-line camera produces an inconsistent optical window around the curvature of the breast skin flap and the internal mobility is limited. Moreover, the dissection angles during endoscopic mastectomy seem inadequate because rigid-tip instruments are working almost in parallel through a single access [5-7]. Because of such technical limits, the endoscopic approach to breast surgery has not been significantly adopted in clinical practice.

Background

In October 2015 Toesca et al [8,9] were the first to describe the surgical technique of single small hidden axillary scar robotic nipple-sparing mastectomy and immediate robotic breast reconstruction with implant.

The aim of this project was to study an innovative technique to improve aesthetic results and patient satisfaction removing the entire breast glandular tissue without disruption to the appearance of the breast, there by overcoming the limitations so far experienced with mini-invasive endoscopic technique.

The surgical technique was published considering the first 3 cases [8] but the same research continued as to evaluate feasibility and safety. The second study was conducted considering 29 consecutive robotic nipple sparing mastectomy and immediate robotic breast reconstruction procedures for patients affected by breast cancer [10].

The early phase of our study was focused on the development of a new technique and the description of its outcomes and not aimed at assessing its effectiveness against current standards but to demonstrate its feasibility, reproducibility, surgical and oncological safety.

Technical Considerations

From a technical point of view, the use of the da Vinci Xi® (Intuitive Surgical, Sunnyvale, CA) system with respect to the classical technique offers certain advantages such as robotic optical 3D vision with a ten-fold image magnification and a better intense lighting view of the proper surgical dissection plane. This enhances the difference in contrast of colors of different structures, thereby highlighting blood vessels, lymphatic vessels, adipose lobules, the crests of Duret, Cooper's ligaments, the mammary gland itself and the skin. Sharpness and clarity of image, associated with a high precision of movement of the instrument, greater stability due to tremor abolition and greater accuracy, permit a better detachment of the gland from its suspensory ligaments. Furthermore, the robotic instruments have 7 degrees of freedom of motion at the tips. Not only does this allow for increased precision in controlling small vessels and maintaining a consistent plane, but it also allows negotiation around the curvature of the breast skin cupola which has been reported as being a limitation of endoscopic instruments [5-7].

Oncological Safety

Oncological safety of skin-envelope preservation has been clearly demonstrated by many studies in which skin-sparing mastectomy and nipple-sparing mastectomy are reported to have a local recurrence rate similar to that of modified radical mastectomy [11-13]. The main issue regarding this new robotic surgical approach is whether preservation of the skin envelope (nipple-areola complex included) amplifies the local recurrence rate. There are in fact many studies which report that different kinds of skin incision do not influence local recurrence rate and that breast skin removal is not necessary when clinically negative [11-13].



Figure 1 and 2: Comparison between robotic vs classical technique 6 months after operation. Right side is a robotic technique, left side is a classical open technique.

In this scenario, we have to consider that after completion of surgical and adjuvant treatment, breast cancer survivors or BRCA mutation carrier women have to cope not only with the fear of future disease recurrence but also with an altered body image that affects their everyday life. In view of the high cure rate of breast cancer, cosmesis and emotional well-being are important, and the availability of new technologies should be of service in this objective.

Total glandular excision is especially important in women with multicentric disease, invasive cancers with extensive intraductal component, or pure extensive ductal intraepithelial neoplasia. In those patients who have small and medium-size breasts, mastectomy is sometimes inevitable to achieve clear margins. Mini-invasive mastectomy could offer a solution for complete excision of mammary tissue, including all ducts in the nipple, with a good aesthetic result.

Cosmetic Outcome

The minimal incision hidden in the axilla, the great respect for anatomical structures during skin and subcutaneous flap detachment lead to high trophism, vitality and unchanged color of the nipple-areola complex. In our opinion, this minimally invasive approach might reduce changes in the woman's body image, thereby increasing patient satisfaction. Robotic mastectomy is a form of conservative mastectomy entailing complete removal of the breast parenchyma, not only in combination with preservation of the breast-skin envelope and the nipple-areola complex, but also avoiding any visible scar on the breast dome (Figures 1, 2 and 3, 4).

From Feasibility Study to a Prospective Randomized Trial

In our opinion this method is sufficiently developed to warrant full evaluation in further cases. The excellent results encouraged us to design a randomized trial



Figure 3 and 4: Example of bilateral robotic nipple sparing mastectomy and immediate robotic reconstruction (5th post-operative day).

comparing robotic nipple sparing mastectomy and immediate breast robotic reconstruction with conventional open technique.

The primary end-point is to evaluate patient satisfaction. Second end-point is to compare post-operative outcome considering complications, post-operative pain, reduction of the average length of stay of patients, long term oncological outcome of the two different surgical techniques.

Randomization into two treatment arms:

- A. Open nipple-sparing mastectomy and immediate breast reconstruction with implant.
- B. Robotic nipple-sparing mastectomy and immediate robotic breast reconstruction with implant.

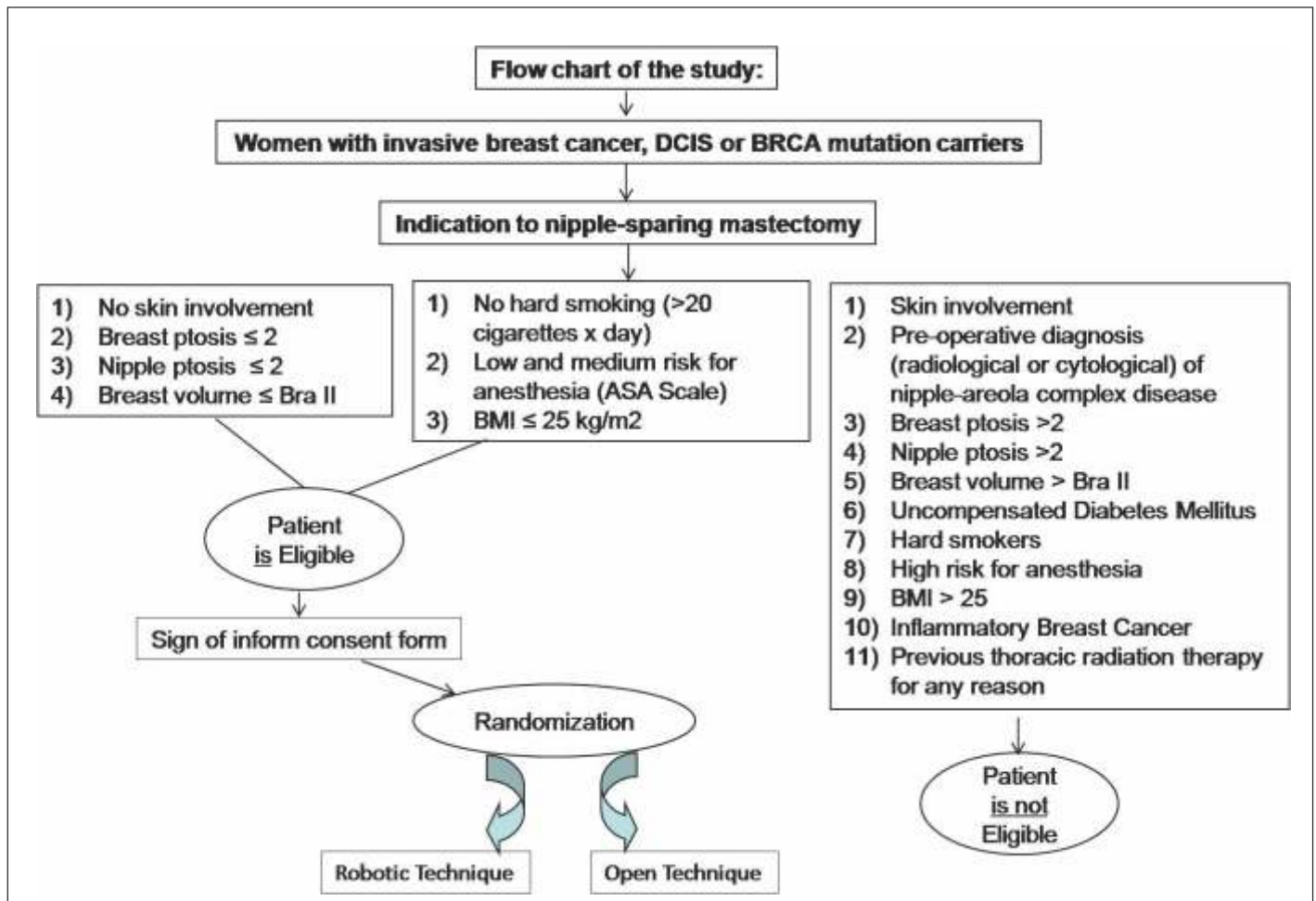
Both arms undergo to the same pre-surgical staging, intra-operative axillary surgical staging, post-operative multidisciplinary evaluation and adjuvant treatments according to international and internal protocols.

The Aim of the Study

- To verify whether, the patients' quality of life can be improved by a less invasive surgical procedure.
- To verify whether, the use of robotic technique for nipple-sparing mastectomy procedure can be more respectful of women image.
- To verify whether, the use of robotic technique can impact on operation time, amount of blood loss, number of conversions to open technique, length of hospitalization, amount of morphine use/pain, number of complications.
- To verify whether, the use of robotic technique can impact on oncologic outcome.

Evaluation of Satisfaction (Questionnaires):

Questionnaire: The BREAST-Q was developed at the Memorial Sloan-Kettering Cancer Center and the University of British Columbia [14]. This instrument specifically



measures patient satisfaction and health related quality of life following different types of breast surgery. This instrument encompasses six scales: psychosocial wellbeing, physical well-being, sexual well-being, satisfaction with breasts, satisfaction with overall outcome, and satisfaction with care. This instrument includes questionnaire items specific to implant breast reconstruction patients (i.e., inability to perform activities of daily life because of pain resulting from capsular contracture of the implant), and how such issues may affect quality of life, postsurgical satisfaction, and body image. Scoring of the BREAST-Q is performed using QScore, which was developed according to the Rasch model [14]. All scales are scored on a 0- to 100-point scale.

Additionally, Hopwood’s body image scale (BIS) [15] consists of 10 questions concerning body image with 4 response options per question: “not at all” (score 0), “a little” (score 1), “quite a bit” (score2), and “very much” (score3). A total score ranging from 0 to 30 is obtained, where 0 represents no distress or symptoms, whereas higher scores represent increasing symptoms and distress.

To assess patient satisfaction with the nipple areola complex, subjective sensitivity, and the role of nipple

areola complex and breast in sexuality, we administered a nipple-areola complex specific questionnaire comprising 12 items that are scored on a 5-point Likert scale [15].

Acknowledgments

The study is in accordance with the IEO Ethical Committee. The registration number is “R 530/16 – IEO 562”.

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CANCER CONTROL

Grilled or Smoked Meats, Even Fish, Can be Risky

A new report highlights the link between grilled or smoked meats and breast cancer. It has been found that meats cooked at high temperatures, as are grilled, barbecued and smoked meats are associated with carcinogenic chemicals like polycyclic aromatic hydrocarbons. Consuming foods with these carcinogens is also linked to breast cancer incidence. The researchers interviewed 1,508 women with breast cancer living on Long Island. They were asked about their consumption of grilled, barbecued, or smoked beef, lamb, pork and poultry/fish during each decade of their lives, and the seasons they most frequently consumed these foods. High intake of grilled/barbecued and smoked meat prior to cancer diagnosis was linked to a 23 percent increase in all-cause mortality compared to low consumption of these foods. High intake of smoked beef, lamb and pork was linked to a 17 percent increase in all-cause mortality, and a 23 percent increase in breast cancer-specific mortality. Overall mortality risk, the research concluded, was similar among women who reported high pre-diagnosis and low post-diagnosis intake of grilled/barbecued and smoked meats, supporting the premise that high consumption of these meats post-diagnosis appears to heighten the risk of death in breast cancer survivors.

(Medscape Medical News, January 17, 2017)

Social Ties and Higher Survival

New research suggested that having a large social network might also affect a person's chances of survival. Since 1990, breast cancer survival rates have been increasing. Due to better screening practices, increased public awareness and early detection, and improved technology and treatments, mortality in women aged 50 and older has been declining significantly for the past 2 decades. Loneliness and lack of social connections increase the risk of premature death. In fact, some studies have suggested that social isolation and living alone increase the risk of mortality by as much as 29 and 32 percent, respectively. Medical records of 9,267 women with breast cancer were investigated in a study in which the median follow-up period was 10.6 years, during which 1,448 cancer recurrences and 1,521 deaths were recorded. Of the 1,521 deaths, 990 were from breast cancer.

(Journal Cancer, Monday 12 December 2016)

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(Dr Antonio Toesca, Consultant Breast and General Surgeon; Dr Paolo Veronesi, Dr Virgilio Sacchini, Dr Andrea Manconi, Dr Nickolas Peradze, Division of Breast Surgery, European Institute of Oncology, Milan, Italy)

OUTLOOK

HEREDITARY BREAST CANCERS

Cancer is a genetic disease i.e. abnormal change (mutations) in the genetic code resulting in uncontrolled growth and spread of the abnormal cells. Most of the cancers (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 occur 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 two 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 following features: 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 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 (offsprings 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.

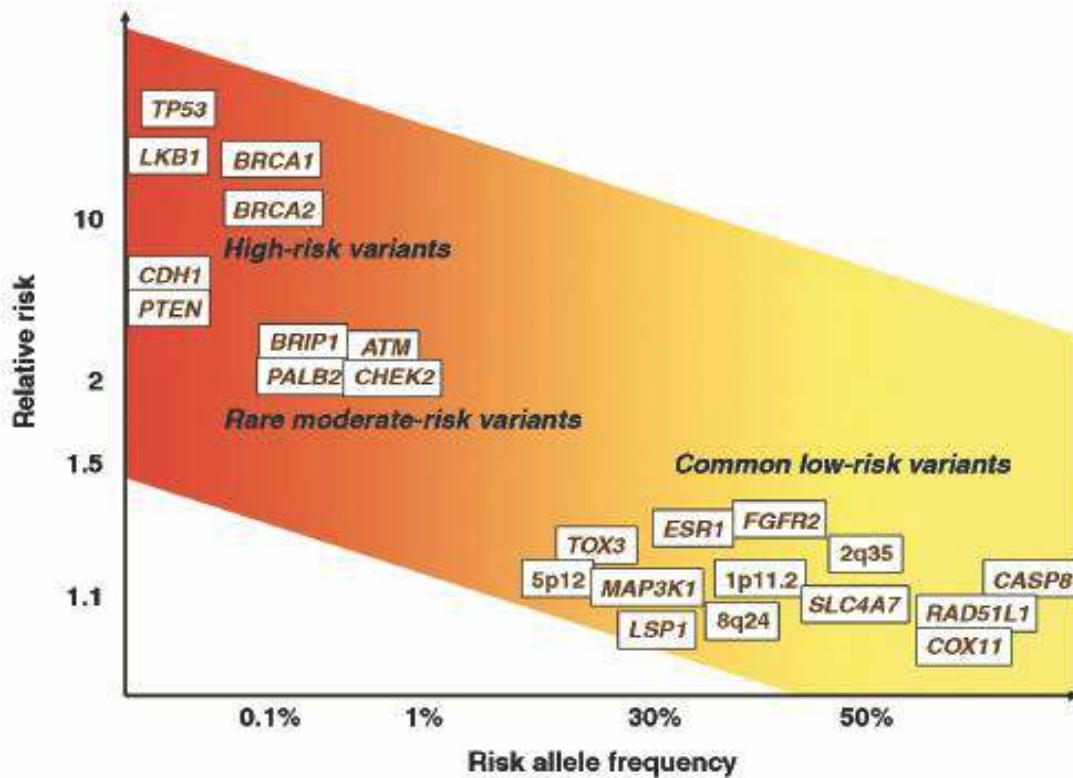
Genetic Variants for Hereditary Breast Cancer

Not all 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 that exhibit clinical symptoms of that disorder. Genetic variants associated with cancer can be broadly classified into the following three categories based upon their penetrance as shown in the figure below:

- High penetrance variants (Rare) BRCA1, BRCA2, TP53, PTEN and STK11gene. The risk of developing breast cancer by age 70 years is 55% to 65% for BRCA1 and 45% to 47% for BRCA2 mutation carriers.
- Moderate penetrance variants (Rare) CHEK2, ATM, NBS1, RAD50, BRIP1 and PALB2 gene. They pose a 2-4 fold increased risk for breast cancer.
- Low penetrance variants (common) - They pose a 1.1-1.4 fold increased risk for breast cancer.

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 (e.g. 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 BRCA 1 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.

Genotype-Phenotype Correlation - Mutation location and genetic variation appear to impact BRCA1 and BRCA2 gene function and play a role in modifying BRCA-associated cancer risks. 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 Counseling and Gene Testing

Cancer Genetic Counseling 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 is carrier 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 both an individual as well as their family members in preventing cancer from developing.

Gene Testing

Techniques: Sequencing is the technique that allows us to look at the individual base pairs and detect point mutations. Two different types of sequencing are used (i) Sanger sequencing (conventional sequencing) and (ii) Next-generation sequencing techniques (NGS). The NGS systems differ from their conventional counterpart in terms of high throughput and more depth of genome coverage per run.

Single Gene Testing and Multi-Gene Panel Testing

Gene testing can be ordered either as a single gene or a panel of breast cancer associated genes (approx. 10-15 genes panel). With the advent of new technology that is NGS, high throughput is possible and multiple genes can be analyzed in a single experiment thus reducing cost and time. The choice depends on the discretion of the physician that varies depending upon the personal and family history of cancer, past known genetic information, strong clinical suspicion for a genetic syndrome, ease of interpretation, acceptance of limitation of testing, availability of the testing facilities, robustness of the respective database, psycho-social degree of readiness etc.

Patients with negative test results based on single genes testing like BRCA1 or BRCA2 gene but with high risk for familial cancer should be offered further testing, as a genetic mutation may be present in other breast cancer associated genes like MMR genes (Lynch Syndrome), STK11 gene (PeutzJeghers Syndrome), PTEN (Cowden syndrome), p53 gene (Li-Fraumeni Syndrome) etc. Multi-gene panel testing may be recommended for such clinical situations.

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 these values may change over time (for example, pre- and post-childbearing). 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 annually beginning at age 25
- Annual breast magnetic resonance imaging (MRI) with contrast between 25 and 29 years of age
- Annual mammogram and MRI with contrast, both should be done between 30 and 75 years of age.
- Annual ovarian cancer screening with transvaginal ultrasound and serum CA-125 levels.

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

- Monthly breast self-examination and annual clinical breast examination starting at the age 35 years
- Appropriate prostate cancer screening starting at the age 45 years

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. Women with a BRCA1 or BRCA2 mutation should consider it.

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.

(Dr Amit Verma, Consultant Molecular Oncology and Cancer Genetics, Max Cancer Center, New Delhi)

NEW TECHNOLOGIES

Mutation Analysis of Cell-Free DNA & Single CTC

Breast cancer in women ranks second in the world in terms of cancer deaths. Next-generation sequencing (NGS) based studies suggest that therapies can induce the evolution of clones of cells that are refractory to the treatment in cancer. Recent studies in breast cancer are concentrating on developing bioassays that help in the selection of therapies as the tumor evolves. These bioassays include characterization of circulating tumor cells (CTC) and the tumor-derived fraction of circulating cell-free DNA (cfDNA) termed circulating tumor DNA. A recent study has shown that it is possible to interrogate both cell-free DNA (cfDNA) and pools of mutation-bearing CTCs from the blood of patients with metastatic breast cancer (MBC). Since cfDNA is easier to obtain than CTCs for molecular analysis, it is crucial to determine whether mutations in cfDNA match that of individual CTCs, as heterogeneity is frequently observed in metastatic biopsies. The present study compared mutation profiles in multiple individual CTCs and matched cfDNA from patients with MBC. In 5 patients multiple individual

CTCs were separated and compared with matched cfDNA for about 2,200 mutations in 50 cancer genes by NGS. NGS analysis of 40 CTCs from 5 patients with MBC revealed mutational heterogeneity in PIK3CA, TP53, ESR1, and KRAS genes between individual CTCs. In the same patients, cfDNA profiles provided similar results suggesting that cfDNA provides an accurate reflection of mutations seen in individual CTCs. Total cfDNA level act as an independent prognostic marker in patients with MBC. These results suggest that cfDNA could potentially enable monitoring of the metastatic burden for clinical decision-making when CTCs cannot be obtained.

(Clin Cancer Res; 23(1); 2016)

Saliva as an Alternative Specimen Source for NGS

Germline mutations in tumor suppressor genes BRCA1 and BRCA2 accounts for approximately 20–25% of hereditary breast cancers, and early diagnosis and preventive interventions result in improved survival rate of mutation carriers. Next generation sequencing is a widely accepted tool for predicting the risk of hereditary cancer development. However, blood as a sample type has many shortcomings such as invasive collection procedure, poor sample stability, and a somewhat higher cost of collection. In the present study, the authors compared the saliva and blood as a source of germline DNA for detecting hereditary BRCA mutations by Ion Torrent next generation sequencing. The results suggested that the quality of DNA from both saliva and blood was comparable. Although the concentration obtained from saliva was slightly lower but both the samples yielded sufficient DNA concentrations for library preparation. The final libraries generated from DNA derived from saliva or blood showed no notable difference in concentration and quality. The alignment of the data obtained from both the specimen sources generated base calls with comparable accuracy. An average of $(98 \pm 0.02)\%$ variant calling concordance was obtained between the two specimen sources. Thus it can be concluded that saliva can be used as an alternative to blood for detecting germline mutations by NGS methods without compromising data quality. The lower DNA yield obtained from saliva may be limiting factor for NGS-based testing, but the present data strongly suggests that at least for some applications, the yield is sufficient to make saliva an acceptable and attractive alternative.

(Int. Journal of Genomics, 26 September 2016)

PERSPECTIVE

HYPOFRACTIONATION IN CARCINOMA BREAST

The evolution in the management of breast cancer often serves as a model for conservative therapy in cancer care, allowing organ preservation. Previously most women with breast cancer underwent removal of the whole breast (mastectomy). However, following a number of large scale, clinical studies, breast conserving surgery (BCS) followed by radiotherapy to the entire breast followed by a boost dose to the lumpectomy cavity, has become the recommended option for women with early breast cancer.

This is one scenario where in addition to achieving locoregional tumor control, a good cosmetic outcome is desirable through appropriate surgical and radiotherapeutic techniques. Surgical techniques including oncoplastic surgeries have been able to achieve this goal and are still evolving.

However, long schedules of conventional radiotherapy (1.8-2 Gy/fraction) spanning over a duration of 6-7 weeks often lead to non-compliance towards treatment or sometimes even reluctance to opt for breast conserving surgery. Gradually Simultaneous Integrated Boost technique with Intensity Modulated Radiotherapy (IMRT) (1.8 Gy per fraction to the whole breast and higher dose of 2.4 Gy per fraction to the lumpectomy cavity) shortened the course to 5-6 weeks. Radiobiological studies suggested

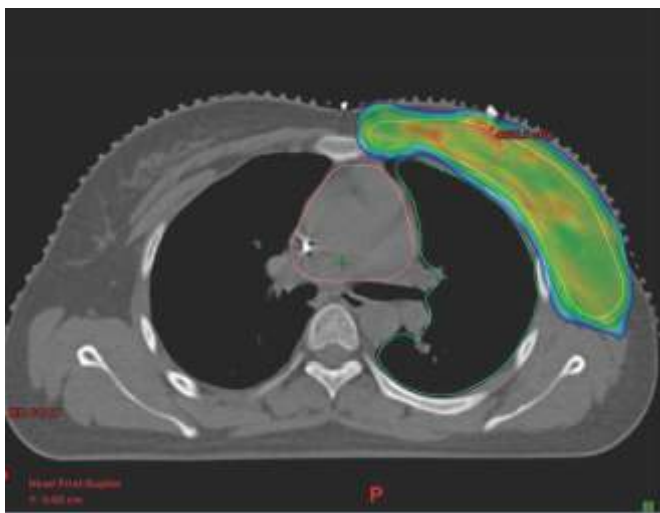


Figure 1: Dose color wash of IMRT plan for whole breast irradiation using hypofractionation showing homogenous coverage of whole breast while sparing of the underlying heart and ipsilateral lung.

that breast tissue is one of the ideal sites to attempt hypofractionation as radiosensitivity of breast cancer is not as dependent on dose per fraction as was previously thought. This approach typically involves 40 to 43 Gy delivered at 2.5 to 2.7 Gy per fraction over 3 weeks.

Hypofractionation for adjuvant irradiation of whole breast after BCS in early breast cancer has caught the fancy of radiation oncologists across the world after the publication of Canadian (published from the continent of North America), START A and B and Royal Marsden (published from the continent of Europe) trials.

Whelan et al (Canadian study) compared the standard dose of 50 Gy in 25 fractions over a period of 35 days (the control group) with 42.5 Gy in 16 fractions over a period of 3 and a half weeks (study group). The risk of local recurrence was same in both the groups with a good or excellent cosmetic outcome after either fractionation schedule.

These were the landmark trials that firmly established the feasibility of short course adjuvant radiotherapy in early breast cancer. Long term results have shown equivalence with conventionally fractionated schedules with respect to locoregional control and cosmesis.

Though American Society for Therapeutic Radiology and Oncology (ASTRO) has issued stringent selection criteria for using hypofractionated radiotherapy schedules, it is being used worldwide in a wide range of cases, even after modified radical mastectomy for irradiation of the chest wall.

However, the above mentioned studies have not elaborated upon the radiotherapy techniques used and any long term effects on the underlying organs at risk. This data is important as an increase in the dose per fraction has an impact on the late reacting normal tissues in the vicinity of the irradiated site, in this case, lungs and heart. It is therefore imperative, that long term follow-up of these patients with respect to pulmonary and cardiac function be evaluated and published. When evaluating cardiac toxicity with hypofractionated regimens, one must take into account the addition of anthracycline based chemotherapy as well as trastuzumab which the patients receive before the initiation of radiotherapy. Similarly, pulmonary toxicity and lymphedema rates must be evaluated in the context of taxane receipt.

Greater caution needs to be executed with the increasing use of IMRT where sharp dose gradients are achieved (Figure 1). The planning and evaluation of radiotherapy plans

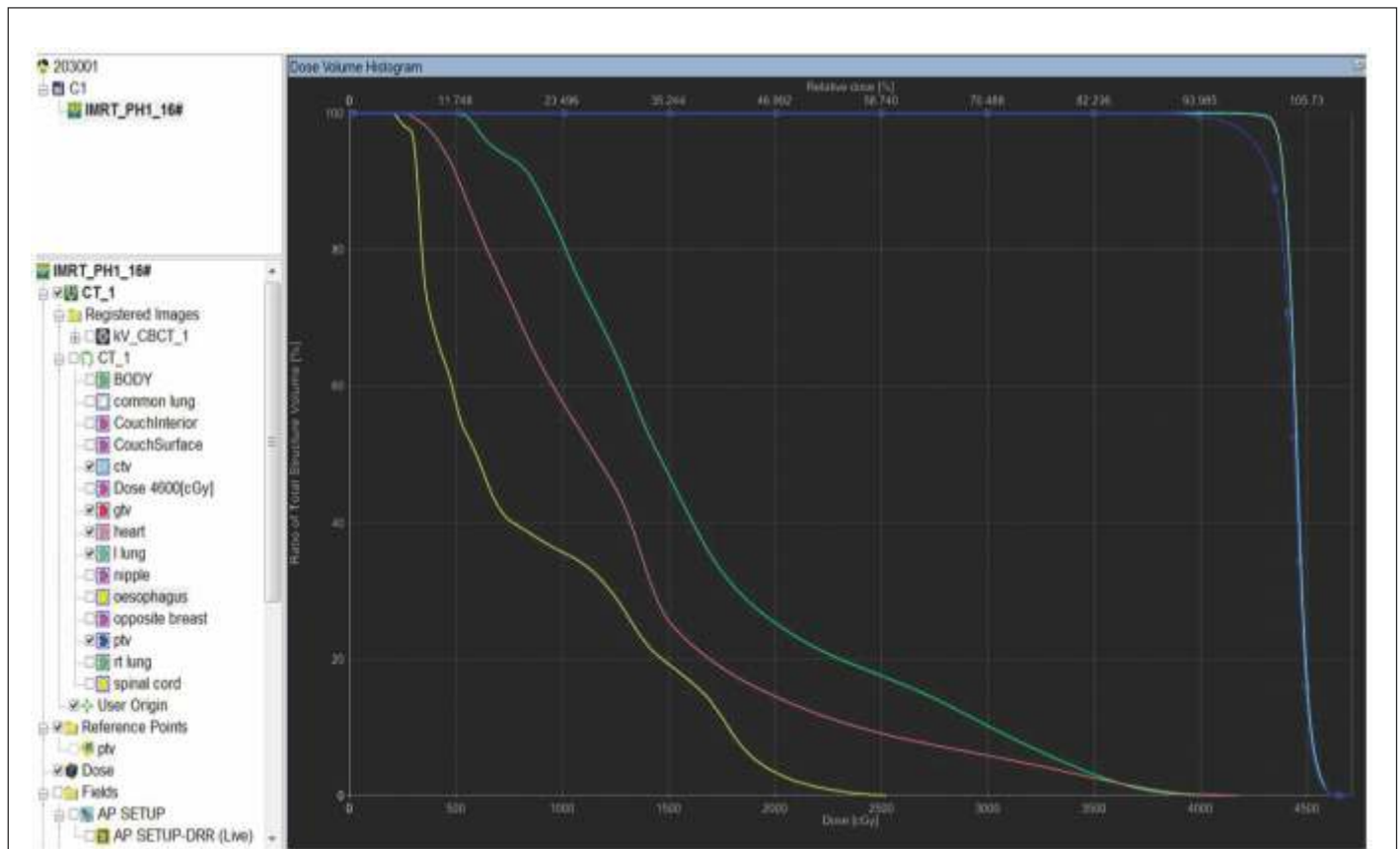


Figure 2: Dose volume histogram of the IMRT plan for hypofractionation showing sharp dose gradients across the target volumes and organs at risk.

has to be done meticulously and any hot spots (very high dose regions) should be avoided near the skin of the breast (Figure 2). Large areas of hot spots near the skin, especially in a hypofractionated course, will have a detrimental effect on cosmesis by causing breast fibrosis and telangiectasia after some years. Hypofractionation should be avoided in large breast volumes as it may hamper long term cosmetic outcome. Therefore, the short term gain with hypofractionation in terms of reduced overall treatment time must be weighed carefully against long term possibility of hampered cosmesis or late side effects on the heart and lung in inappropriately selected cases.

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). 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 (Figure 3).

How about hypofractionation in regional nodal irradiation (RNI)? So far robust data (highlighted above) exists about use of hypofractionation in whole breast irradiation but limited data exists on using it for RNI. Retrospective reviews of subset of patients whose regional nodes were included in the hypofractionated radiation fields have not shown an increase in the incidence of pulmonary or cardiac toxicity or brachial plexopathy.

Now what is the scenario of hypofractionation in India? The last decade has seen an alarming rise in the incidence of breast cancer amongst young females in the age group of twenty five to thirty five years. Women in this age group have varied roles to play in the Indian ethos, from being a homemaker to a bread winner for the family. Surgery followed by adjuvant chemotherapy and further followed by a 6-7 weeks of radiotherapy meant loss of job hours for those professionally employed and compromising home and child care for the housewives. With scarcity of good radiotherapy centers across the country, logistic issues pertaining to daily commuting or arranging accommodation near a radiotherapy centre along



Figure 3: Interstitial brachytherapy for delivering APBI

with the financial burden for a duration of 6-7 weeks can be a limiting factor for many to complete their prescribed course of radiotherapy. So, there is no doubt that hypofractionation has been a boon for these patients. However, we would like to reiterate on the need for longer follow-up of these patients with respect to cardiac and pulmonary function, as this particular profile of younger females tend to have high risk disease requiring taxanes and anthracyclines in the adjuvant treatment.

In a prospective, randomized study involving 50 patients with early breast cancer, recruited from 2014 to 2016 at Rajiv Gandhi Cancer Institute and Research Centre, who had undergone breast conserving surgery were randomized to receive adjuvant radiotherapy by SIB or hypofractionation (hypo) with sequential lumpectomy boost.

Harvard scoring was used for grading cosmesis. At 3 months post radiotherapy, excellent score was higher in the SIB arm (20 %) than hypo arm (8 %), good score was higher in SIB arm (44 %) than hypo arm (40 %), and fair score was higher in hypo arm (52 %) than SIB arm (36 %). However, these differences were not statistically significantly different ($p = 0.357$).

There was slight change in the cosmesis in patients post 6 months with excellent score post BCS. There was decrease in cosmesis score post radiotherapy in both the arms but cosmesis improved in hypofractionation arm

after 6 months of radiotherapy with increase in number of patients with good score and decrease in fair score. There was deterioration in the Harvard score in the SIB arm post 6 months RT with maximum number of patients with fair score. However, there was no statistical difference in either of the arms.

We at RGCIRC, do give an option of hypofractionation to suitable patients. However, IMRT plans are generated using both SIB and hypofractionation schedules. The plan which is implemented on the patient will be the one which gives the maximum therapeutic benefit in terms of target volume coverage and sparing of organs at risk with minimal hot spots near the surface of the breast.

Hypofractionation is a good tool in the hands of a radiation oncologist for carefully selected patients when combined with meticulous attention to contouring near the skin and axillary region and careful plan evaluation. Its use in routinely irradiating chest wall has not been published widely and should be used exceptionally.

Hypofractionated whole-breast irradiation offers an opportunity for improved patient convenience, lower healthcare costs, better utilization of radiotherapy resources and greater access to care without sacrificing outcomes.

(Dr S K Sharma, Senior Consultant; Dr Anjali Pahuja, Consultant; Dept of Radiation Oncology, RGCIRC)

IN FOCUS

ONCOPLASTIC BREAST CANCER SURGERY: AN OVERVIEW

Introduction

Each year 1.15 million new cases of breast cancer are being added all over the world. In our country, the disease has steadily grown in the past few decades. There were 155,367 new cases of breast cancer in the year 2014 and more than 60,000 deaths due to breast cancer in India, not taking into account those that go unregistered. Also, breast cancer in India is affecting comparatively younger women and more than half of the cases are detected at advanced stage. Indian women are getting entangled in this rising menace of Breast Cancer when they are in their most productive phase of life cycle.

The fight against breast cancer can be won, if women end up sacrificing their breast and losing their femininity. The answer to this has been provided with the evolution of techniques of Oncoplastic breast Cancer Surgery, which involves resection of Breast cancer along with neo (new) breast formation, either in form of breast preservation (conservation) or Breast Reconstruction. Oncoplasty in other words, means amalgamation of techniques of breast cancer resection and aesthetic breast correction providing safer cancer removal and preservation/reconstruction of breasts.

The goals of Oncoplastic Breast Cancer Surgery are:-

1. Optimum cancer resection without any compromise on oncological principles. In fact, oncoplasty helps to achieve

better margin control leading to better cancer resection.

2. Optimum Neo Breast Formation. In fact, oncoplasty aims to provide aesthetically better breast. ‘The new one should be better than the old one’.

In addition to providing superior cosmetic results, oncoplastic surgery also holds another benefit over traditional breast cancer surgery for women with large breasts. The radiation therapy used to treat breast cancer is more difficult for women with large breasts. Removing excess breast tissue through oncoplastic surgery reduces the complications of radiation therapy in these women.

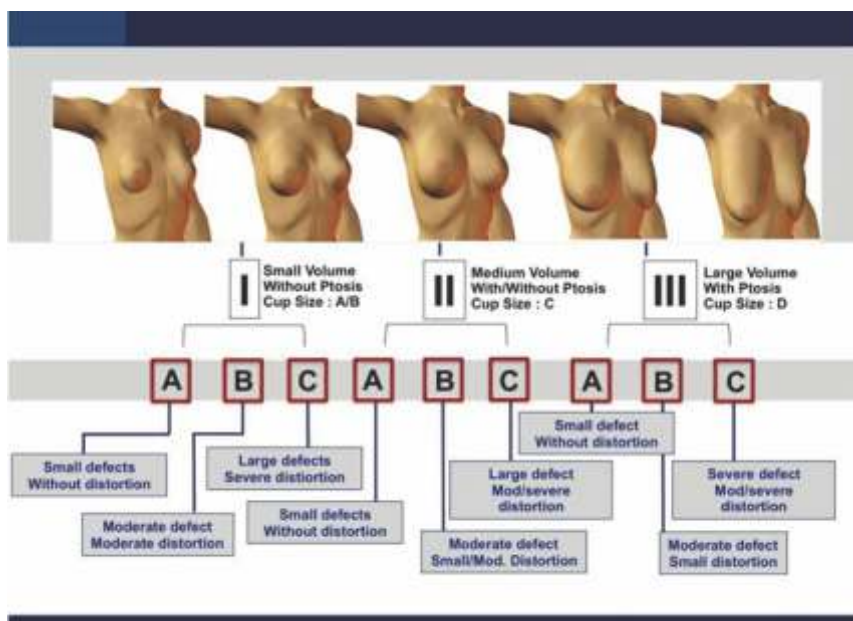
The Breast Oncoplastic Service is defined as a core component of the breast multidisciplinary team with sufficient experience to offer patients access to the full range of procedures encompassed by oncoplastic breast reconstructive surgery, which include:

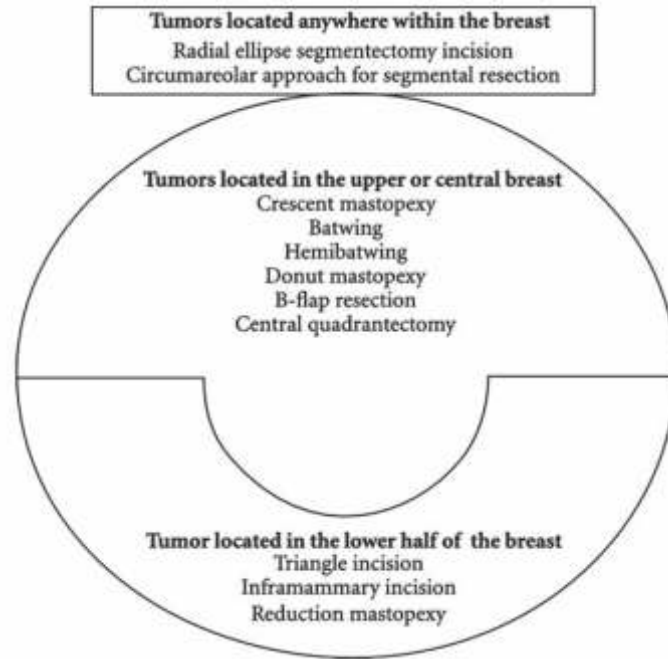
- Appropriate adequate surgery to extirpate the cancer
- Partial reconstruction to correct wide excision defects
- Immediate and delayed total reconstruction with access to a full range of techniques
- Correction of asymmetry of the reconstructed and the contralateral unaffected breast.

Indications

Breast-conserving surgery and reconstruction should be considered in those patients where adequate local excision cannot be achieved without significant risk of local deformity. This frequently occurs after:

- Resection of more than 20% of the breast volume;
- Central, medial and lower pole resections;





- Axillary dissection through lumpectomy incision;
- Periareolar incisions in inferior quadrants;
- Incomplete mobilisation of breast parenchyma to allow reshaping of the breast.

Contraindications

Breast-conserving reconstruction is contraindicated:

- When clear margins cannot be assured without performing a mastectomy;
- In patients with T4 tumours;
- In those patients with multicentric disease;
- In patients with extensive malignant mammographic microcalcification;
- In patients with inflammatory carcinoma.

Oncoplasty has two approaches, Volume Displacement and Volume Replacement.

Volume Displacement

Volume Displacement is a form of Breast Preservation, and the technique is utilized after lumpectomy or partial mastectomy when the residual defect (after cancer resection) is 30% or more of the original breast volume. This situation normally occurs when there is low volume disease and/or with females having large breasts. The Neo Breast formation occurs by mobilizing and reshaping the residual or remnant breast into new and better breast. The surgery is properly planned with the help of 3D virtual reconstruction of MRI or PET CT images, such that the tumor resection is performed as per the principles of

Mammoplasty (Aesthetic Breast Surgery). The remnant tissue is then re-shaped into a new breast using techniques of Mastopexy (Breast Lift) during majority of times.

There are different techniques depending on the size and site of tumor, age of patient, type and nature of breast. They are enumerated as following:-

- Glandular remodelling
- Inferior pedicle techniques
- Superior pedicle techniques
- Vertical scar techniques
- Round block techniques
- Grisotti flaps

Volume Replacement

Volume Replacement Oncoplasty, comprises of surgical techniques utilized for Neo breast Formation when the residual defect formed after cancer resection is 30% or more of the original volume. The Neo Breast formation occurs by replacing the lost breast tissue from other portions of the body. It consists of harvesting tissue from other sites of the body and transfer the tissue onto the ablated breast site to form the Neo Breast using the technique of either pedicled or free tissue transfer. The most common sites of tissue harvest are either from back or lower abdomen. The tissue from the back is harvested in form Latissimus dorsi Myocutaneous or Adipofacial flap with blood supply from Thorcodorsal Vessels known as LD reconstruction. It is a pedicled form of tissue transfer suitable for partial mastectomy defects.

In cases of low or small volume breasts, it can be used to fill complete mastectomy defects. The lower abdomen tissue harvest is in form of adipofacial or adipocutaneous tissue with blood supply from Deep Inferior Epigastric Vessels. It is a free tissue transfer, which means that tissue is harvested along with the blood vessels and these blood vessels are anastomosed with recipient blood vessels in the breast defect or axilla using techniques of microvascular surgery. It is best suited for complete mastectomy defects. The woman gets rid of her breast cancer, gets a new breast and also gets a tummy tuck.

Nipple-Areola Reconstruction

The final part of the breast reconstruction is the reconstruction of the nipple - areola complex. Some patients are happy with a prosthetic nipple but patients should be offered the opportunity to proceed to nipple reconstruction. Techniques for nipple reconstruction are

- Prosthetic nipple
- Composite grafts
- Local flap reconstructions (multiple designs)

Techniques for Areola Reconstruction

Tattoo Full thickness skin grafts Skin grafting has been abandoned largely in favour of tattooing, a relatively simple technique with few complications. Improved colour match can be achieved by the use of a 3D colour-chart.

Decisions about reconstructive surgery must:

- Not compromise oncological principles;
- Consider risk factors evident in the individual concerned, particularly smoking, obesity, diabetes, hypertension, co-morbidity and complications of previous surgery such as deep vein thrombosis;
- Take into account the potential delay in adjuvant treatment which may occur as a result of complications;
- Consider how adjuvant treatment may adversely affect the outcome of reconstruction.

These techniques have made breast cancer surgery, a happy surgery bringing new zeal to life.

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GLOBE SCAN

Microsurgical Breast Reconstruction

Enhanced recovery pathways (ERPs) have been shown to aid in patient recovery and improve outcomes in many surgical settings. The authors sought to assess patient outcomes before and after the introduction of an ERP that was adopted by multiple surgeons at a single cancer center. A multidisciplinary ERP was developed for patients undergoing deep inferior epigastric perforator (DIEP) or muscle-sparing free transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction. The primary endpoints were hospital length of stay (LOS) and total postoperative opioid consumption. Mean hospital LOS was significantly shorter in the ERP group than in the pre-ERP group (4.0 vs 5.0 days; $p < 0.0001$). Total postoperative morphine equivalent consumption was also lower in the ERP group (46.0 vs 70.5 mg; $p = 0.003$). The adoption of an ERP for DIEP and TRAM flap reconstruction by multiple surgeons significantly decreased opioid consumption and reduced LOS by 1 day.

(USA: *Plast Reconstr Surg*, Jan 12, 2017)

Breast Cancer in Cameroon

In Cameroon, patients with breast cancer are more often diagnosed at stage III and IV, hence the need of preventive actions. The objective was to describe the knowledge, attitude, and practice of health care professionals on breast cancer risk factors, diagnostic methods, and screening. A cross-sectional study was conducted during a 6-month period, among health professionals of Douala General Hospital and Laquintinie Hospital, Cameroon. Data were collected using a self-administered questionnaire. Participants fell in four categories of knowledge, attitude, and practice: very weak, weak, good, and excellent. Overall, 445 health professionals were interviewed. The level of knowledge, attitude, and practice was assessed respectively as weak (50.1%), very good (64.5%), and poor (36.4%). After multivariate analysis, the factor associated with good to excellent knowledge was the participant qualification (academic degree). These results suggest the need for training of health professionals in Douala reference hospitals.

(Cameroon: *J Cancer Educ*, Jan 13, 2017)

ABSTRACTS OF RGCIRC

TAILORED APPROACH TO MANAGEMENT OF BILATERAL BREAST CANCER IN INDIAN WOMEN:

Veda Padma Priya Selvakumar, Shubha Garg, Kahkash Siddiqui, Ashish Goel, Kapil Kumar, Rajeev Kumar. Tailored Approach to Management of Bilateral Breast Cancer in Indian Women. Asian Journal of Oncology. 10.4103/2454-6798.173311.

Introduction

Bilateral breast cancer BCC is relatively uncommon with an overall incidence of 5-20% in women with early breast cancer. They are divided into synchronous if cancers are detected simultaneously or within 6 months of each other and metachronous if they are detected more than 6 months apart from each other. Family history and hereditary cancers multicentricity and lobular histology are some of the factors associated with BCC. In this background, we sought to evaluate the incidence, clinicopathological profile, and management of women with bilateral primary breast cancer at our institute.

Materials and Methods

We retrospectively reviewed the medical records of women who underwent surgery for BCC at the breast services unit at our institute from October 2010 to April 2015. The clinicopathological profile and outcomes were analyzed using SPSS 22 software and appropriate statistical tests.

Results

Out of 1330 women who underwent surgery for early breast cancer between October 2010 and April 2015, 44 were bilateral. 28 were synchronous and 16 were metachronous. Mean age of the presentation of patients was 53 years (range 30-79 years). The histological types were same in 82.14% of synchronous tumors and 87.5% of metachronous tumors ($P = 0.496$). The grades were similar in 42.85% of synchronous tumors and 56.25% of metachronous lesions ($P = 0.294$). The stage concordance among synchronous tumors was 39.28%, whereas it was 60% among metachronous lesions ($P = 0.164$).

Conclusions

The management of BCC is complex and has to be tailored to the individual based on characteristics of index and second tumor, prior therapy, adjuvant treatment, and risk stratification. Moreover, the concordance of receptor expression is higher in synchronous cancers than metachronous cancers.

METAPLASTIC CARCINOMA BREAST - A PRACTICAL DILEMMA, 5 YEAR TERTIARY CANCER CENTER EXPERIENCE: Dr D C Doval, Dr Juhi Tayal

Background

Breast cancer is a heterogenous disease of multifactorial origin. The etiological journey begins in utero and continues throughout life with a variety of exposures modulating the risk at different times. Metaplastic breast cancer (MpBC) is a unique and rare histological subtype and accounts for less than 1% of all breast cancer. This category of breast malignancy encompasses tumors in which adenocarcinoma is found to coexist with an admixture of spindle cell, squamous, chondroid or bone forming neoplastic cells. At the molecular level MBC's cluster with triple negative breast cancers (TNBC's), but have a worse prognosis than TNBC's.

Aim & Objectives

A retrospective analysis to evaluate the prevalence, clinicopathological and treatment variables, and furthermore evaluate response to treatment in terms of overall survival (OS).

Material and Methods

Histopathology reports, clinical records of the patients diagnosed with breast cancers during 2008-2012 at Rajiv Gandhi Cancer Institute and Research Centre (RGCI & RC) were screened and patients with MpBC were identified as per the histological definition of WHO. Variables like pathological diagnosis, staging, hormone receptor, Her2Neu status; epidemiological details, clinical features and management were noted. Categorical variables were presented in number and percentage (%). Kaplan Meier Survival analysis curve was used to find out overall survival and recurrence free survival rate at 4 years for deciding treatment outcomes.

Results

A total of 2240 cases of breast cancer presented in a single unit of RGCI between the years 2008-2012. 96 cases (4.15%) of rare subtypes were identified. MpBC constituted a total of 9 female patients, with an average age of 54 yrs (range = 41-65 years) and tumor size 5.4cm (range = 2.2-15cm). 2 cases presented with locally advanced disease and 1 case with distant metastasis to

ABSTRACTS OF RGCIRC

lung. Various histopathological presentations were as follows-2 Squamous differentiation, 2 adenosquamous, 2 with chondroid differentiation, 2 with chondrosarcomatous and 1 with sarcomatoid differentiation. Lymphnode positivity was seen in 4 out of 9 cases. All 9 patients were triple negative (ER/PR/Her2neu). All patients underwent surgery and chemotherapy. Chemotherapy protocols were anthracycline, taxane and platinum based and were planned in neoadjuvant (NACT) and adjuvant settings. 3 patients received NACT and 6 Adjuvant chemotherapy. Of the 9 cases 6 patients underwent Radiotherapy (66%). Average follow up was 50.7 months (Range = 21-96 months). 1 of the 9 patients died with an OS of 21 months. 8 patients (89%) are alive without disease (DFS) in this cohort.

Conclusions

The findings in this series in terms of treatment response, OS and DFS varies drastically from that in literature probably due to early stage presentation and a combined modality approach in most of these cases.

RARE TUMORS OF THE BREAST: A ROAD LESS TRAVELLED: Dr D C Doval, Dr Juhi Tayal, Dr Anurag Mehta, Ms Atika Dogra, Alok Kumar

Context

Breast tumors constitute a diverse group of morphological phenotypes and specific histopathological types with particular prognostic and clinical characteristics. However, there are more than a dozen variants which are less common but still very well defined by the World Health Organization (WHO) classification. Rare tumors of the breast constitute less than 2% of all breast cancers. Given the rarity of these tumors, the literature primarily contains case reports, small series and population based studies.

Aim & Objectives

Identification of the rare histological types of breast cancer, descriptive analysis of clinical and pathological variables and evaluating response to treatment with respect to overall survival (OS) and disease-free survival (DFS) at 4 years.

Study Design and Methods

Retrospective data of patients with breast cancers during 2008-2012 at Rajiv Gandhi Cancer Institute and Research Centre (RGC & RC) was screened. The rare histological

subtypes were identified as per the WHO classification. The clinical records of all identified cases were reviewed for complete pathological diagnosis and staging, hormone receptor and Her2Neu status; epidemiological details, clinical features and management. The treatment outcomes were determined by calculating disease free survival (DFS), overall survival (OS) at 4yrs using Kaplan- Meir method. Categorical variables were presented in number and percentage (%). Kaplan Meier Survival analysis curve was used to find out overall survival and recurrence free survival rate and log rank test was used to compare survival and recurrence free survival rate between different parameters. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 96 cases of rare subtypes representing 4.15% of the total 2240 breast cancer cases were reported. The most common morphology observed in the series were mucinous carcinomas (36.5%), followed by papillary neoplasms (14.6%) and medullary carcinomas (13.5%). The tumors of rare histologies presented mainly as early stage disease (79.2%) with 87.9 % of the patient cases at the age of \leq 50 yrs. The early stage cancers showed a higher degree of lymphnode negativity (94.7%) and hormone (ER/PR) receptor positivity (60.4%). The triple negative tumors constituted 27.1% of all the tested cases with majority occurring in medullary and metaplastic subtypes. Median OS in this study group was observed to be 53 months. Overall median DFS = 53 (95% CI: 44.6-61.4) months, 24 months DFS = 92.6%, 60 months DFS = 32.9%. The median OS in patients treated with surgery-only was 60 months and most of them were in early stage in comparison with patients treated with a combination of surgery, chemotherapy and RT wherein the median OS was 37 months which was found to be statistically significant ($p < 0.0001$).

Conclusion

The treatment of rare malignant lesions is frequently controversial due to the absence of trials to determine the optimal managements. This study describes the spectrum of rare breast tumors indicating the clinical, epidemiological and treatment characteristics.



APPEAL FOR FUNDING RESEARCH

Rajiv Gandhi Cancer Institute & Research Centre (RGCI & RC) is a 300 bedded super specialty cancer care centre, with state-of-the-art diagnostic and therapeutic facilities and world renowned medical faculty. It makes a great example of a “not for profit organization” supplementing government efforts in the area of healthcare. We have treated more than 2, 00, 000 patients since inception, and currently admits over 20,000 patients annually. Unfortunately, almost 70% of them come to us in very advanced stages of the disease.

Today, a lot of cancers are curable, provided they are detected early. We would be doing a great service to humanity, if we could detect cancers early. Through camps in underserved areas, we currently screen over 10,000 patients annually, with excellent results in relation to early detection. These outcomes have encouraged us to substantially step up our efforts.

Research is the best defense against cancer. The investments in cancer research and biomedical science during the past four-plus decades have produced remarkable progress in the understanding of the events which initiate a number of cancers at the molecular, cellular and tissue levels. Advances in cancer research are now transforming patient care.

Cancer research often makes the biggest headlines when it begins to benefit patients - but in order to come up with innovative approaches to cancer treatment, we need first to make exciting scientific discoveries that illuminate our understanding of cancer.

RGCI&RC believes that to defeat cancer it's essential that we carry out research on this disease in tandem with translational and clinical research. What's more, we believe that all of our research needs to be integrated closely with the care of cancer patients.

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1. **To enhance our understanding of cancer and help us find and develop better, more effective treatment.**
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A single discovery can take decades. Sometimes it throws up new questions that, in turn, can take a decade to answer. Cancer's a complex question, and there are no easy answers. It's vital that the efforts of medical researchers around the world are supported with continued funding.

We would like to inform you that RGCI & RC is exempted under section 80G and section 35 (i) (ii) of the Income Tax Act. Your donation will be eligible for Tax deduction under section 80G of the Income Tax Act. We are also exempted under section 35(i) (ii) of the Income Tax Act, and 175% of your donation towards scientific research will also be eligible for tax exemption.

We will be happy to discuss the proposal and make a presentation to your CSR Committee (required under the new Company Rules), at a convenient time & date. We solicit your help in our venture and look forward to a positive response.

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E mail: jaitley.swarnima@rgcirc.org



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