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From the Desk of Director Research

Breast cancer is a heterogeneous disease and the most common invasive cancer in females worldwide. The incidence of breast cancer is increasing in the developing world, including India, as 115,000 new cases are diagnosed per year and it is estimated that it will become 250,000 by 2015. The exact cause of breast cancer is not known but certain risk factors are linked to the disease, i.e. early menarche, late child bearing, fewer pregnancies, breast density, reduced duration of breast feeding, use of hormone replacement therapy as well as increased detection through mammographic screening. Breast cancer has also genetic links like BRCA1 and BRCA2 genes which in normal state prevent cancer by creating proteins that keep cells from growing abnormally. However, if mutated these genes are inherited and may be responsible for developing cancer during lifetime, generally at a younger age, before menopause. The overall 5-year survival for breast cancer is almost 89% in United States. In India, this figure is not even more than 60% as more than 50% patients present in stages 3 and 4 disease and have poor prognosis despite aggressive treatment.

There are several treatment options for patients diagnosed with breast cancer, such as surgery, chemotherapy, radiotherapy and hormonal therapy, but the appropriate treatment depends on the stage of disease and risk profile. With the passage of time treatment has been changed. Recent advances in the surgical management of breast cancer follow the basic template of more conservative surgical resections. A paradigm shift has occurred in chemotherapy from classic CMF to anthracycline-based regimens, to the subsequent incorporation of taxanes, administration of dose-dense regimens, and, most recently, the use of targeted therapies. Targeted therapies may be more effective than other types of treatments, as they target the particular group of cancer cells and destroy them without affecting the normal healthy cells thereby minimizing side effects.

Breast cancer is set to overtake cervical cancer as the most common cancer in India by the year 2020. Early detection is the key in the treatment of breast cancer and it can be done by raising awareness, educating women about breast self-examination and clinical breast examination by a health professional, at least every 3 years. Women at 40 and older should undergo screening mammogram every year.

This issue of Cancer News is based on the theme of Breast Cancer, and includes regular articles under the sections "Special Feature", "Guest Article", "Perspective", "Research & Development", "New Technologies", "Clinical Trials", "Watch-Out", "Globe Scan", "Cancer Control" and "In Focus".

We appreciate the contribution made by Dr Ashwini Budrukhar, Associate Professor, Radiation Oncology, Tata Memorial Hospital, Mumbai for providing the "Guest Article".

Suggestions/ comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

ONCOPLASTIC BREAST SURGERY– A REVIEW

Introduction

Ever since William Halsted described the radical mastectomy in 1882, the surgical management of breast cancer has evolved remarkably. There has been a paradigm shift from more radical to conservative approaches. This shift is apparent both in the oncological perspective as well as in the aesthetic point of view. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, a federally sponsored clinical trial that compared segmental mastectomy (lumpectomy) plus axillary dissection, with or without irradiation of the breast, with total mastectomy plus axillary dissection for women with stage I or II breast cancers 4 cm in size (tumor, node, metastasis classifications, T1 or T2, N0 or N1, M0), reported no difference in overall survival in 1985 and updated in 1989. Breast conservation surgery became the standard of care in early breast cancer.

The increasing trend in breast conserving surgery from 40 % in the 90s to 60 % in the 2000s brought forth a whole array of cosmetic problems. Even though the breast tissue is preserved, its shape becomes compromised, resulting in significant contour deformities, breast asymmetry, and poor aesthetic outcomes. Up to 30 percent of women will have a residual deformity that may require surgical correction, which is often difficult. The whole purpose of preserving the breast is defeated. At the same time mastectomy with reconstruction was not warranted in such patients.

Clough neatly summarises the pre-OBS era with his ‘two-bullet rifle’ concept whereby a tumour can either be satisfactorily treated with breast conserving therapy (BCT) or it cannot and mastectomy is the alternative. Cochrane et al, showed that an aesthetically acceptable limit for BCT was approximately 10% volume excision. Wider the excision lesser the cosmesis. This brought forth the clash of interests between sound oncological control and good aesthetic outcome. The oncoplastic scissors thus formed the basis of amalgamation of breast conservation and reconstruction coined oncoplastic surgery by Werner Audretsch from Dusseldorf in 1998. The oncoplastic breast surgery involves appropriate oncologic surgery, immediate homolateral reconstruction

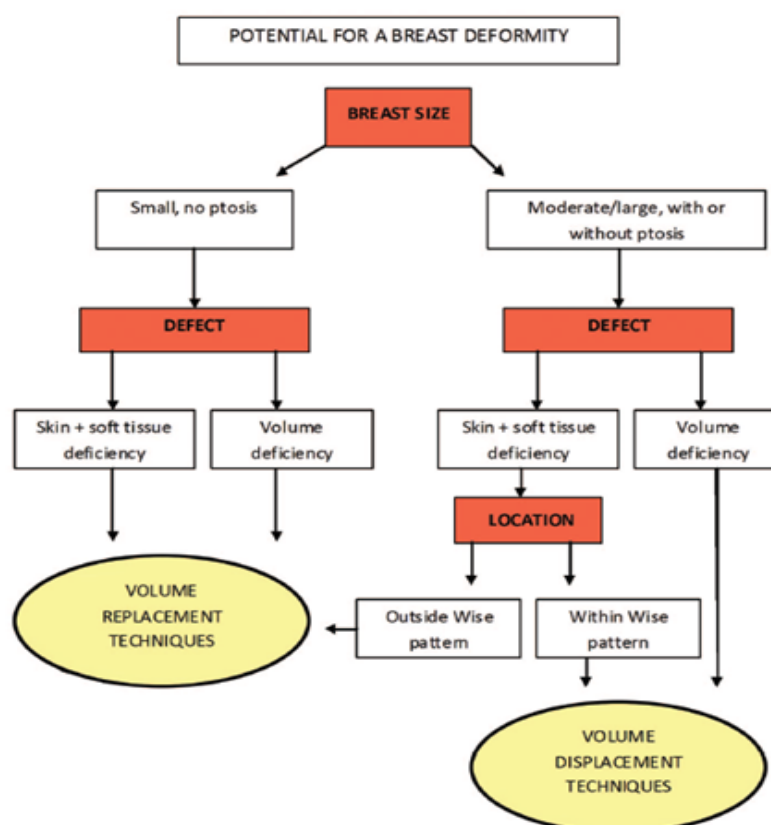


Figure: Reconstructive algorithm base tumor, size, location and defect

Table 1: Classification of the Partial Mastectomy Defect with Potential Outcome and Treatment Options

| Type | Description | Potential outcome | Treatment |
|-------------------------|---|--|--|
| Type 1 (favorable) | Small peripheral defect; large or small breasts | Breast shape is preserved with acceptable symmetry | Primary closure, BAF |
| Type 2 (unfavorable) | Medium to large defect; central defects | Size and shape deficiency with noticeable distortion and asymmetry | |
| Type 2a | Small breasts \pm ptosis | | Volume replacement procedures |
| Type 2b | Medium to large breasts \pm ptosis | Quadrantectomy defect outside standard Wise pattern Any lumpectomy defect Quadrantectomy defect within standard Wise pattern Major deficiency | Volume replacement technique Volume displacement techniques |
| Type 3 (unfavorable) | Extensive resection with little remaining breast tissue; large or small breasts | | Mastectomy and reconstruction |

BAF, breast advancement flap.

using plastic surgery techniques, and correction of the contralateral breast, whenever a symmetry procedure is required. The conclusions of the recent Milanese Consensus Conference on Breast Conservation were that oncoplastic techniques are warranted to allow wide excision and clear margins without compromising cosmesis. Secondly, such surgery is ideally performed at the same time as oncological excision.

The advantages of oncoplastic breast surgery are :

1. More extensive resections are feasible including larger tumors which previously required mastectomy
2. Attaining wider margins of resection.
3. Better dose homogeneity for radiation.
4. 40% risk reduction when more than 400gms are resected.
5. Central and inferior quadrant tumors can be offered breast conserving surgery.
6. Patients with larger & ptotic breasts are benefitted with mammoplasty.

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 tumors;
- in patients with multicentric disease;
- in patients with extensive malignant mammographic microcalcification; and
- in patients with inflammatory carcinoma.

Once the tumor resection is done, the post excisional defect is assessed. Tumor parameters, breast shape and size are analysed. When the parenchymal resection is greater than 70 -100cc, the cosmetic outcome tend to decline. There are two fundamental types of reconstruction: volume displacement and volume replacement. Losken et al have proposed a modified Clough's classification of the partial mastectomy defect with the potential outcome and treatment options. Type 1 defects are favourable small peripheral defects in small or larger breasts. Primary closure or breast advancement flaps are a suitable treatment option and the cosmetic outcome is good. Type 2 defects are medium to large or central in small (2A) or large (2B) breasts. 2A defects can be managed with volume replacement techniques while 2B defects are suitably managed with either volume displacement or replacement. Type 3 defects are large unfavourable defects in small or large breasts and are best managed with mastectomy and reconstruction.

Table 2: Partial Mastectomy Reconstruction Techniques

| Volume Displacement Techniques | Volume Displacement Techniques |
|--|--|
| Parenchymal remodeling, Volume shrinkage Primary closure | Adjacent or distant tissue transfer, volume preserving |
| Mirror biopsy/excisions; batwing mastopexy | Implant augmentation (rare) |
| Breast flap advancement techniques | Local flaps (fasciocutaneous, perforator, and latissimus dorsi myocutaneous flaps) |
| Nipple-areola centralization Reduction mastopexy techniques | Distant flaps |



Fig 1: fasciocutaneous flaps

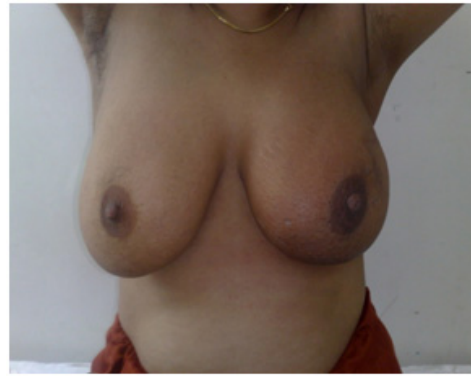


Fig 2: LD flaps for central quadrant tumors

Fig 3: block technique



Fig 4: wise pattern reduction mastopexy technique

Volume Displacement Techniques

BAF: Breast advancement flap is mobilizing the breast plate from the area immediately around the defect. A full-thickness segment of breast fibroglandular tissue is advanced to fill the dead space. It is suitable for 2B defects and a contralateral symmetrization is usually not required.

Reduction mastopexy lumpectomy: This is a modification of the reduction mastopexy technique with the inferior based flap deepithelialised and advanced superiorly.

Volume Replacement Technique

Local fasciocutaneous flaps: Clough et al described subaxillary flap for lateral quadrant tumors. This can be applied for small lateral defects. Munhoz et al has described lateral thoracodorsal transposition flap for lateral defects.

LD myocutaneous flaps: The latissimus dorsi musculocutaneous flap is a common local option for lateral, central, and even medial defects. Mini LD is another excellent option for lateral defects.

Conclusions

The benefits of using the oncoplastic approach with breast conservation therapy have been well demonstrated and will continue to gain popularity and acceptance in the future. The options for women with breast cancer are numerous, and this approach provides an additional, often favorable one.

(Dr S Veda Padma Priya, Consultant, Dr Ashish Goel, Consultant, Dr Kapil Kumar, Sr Consultant, Dept of Surgical Oncology; Dr Sandeep Mehta, Sr Consultant, Dept of Reconstructive Surgery)

GUEST ARTICLE

ACCELERATED PARTIAL BREAST IRRADIATION: CURRENT SCENARIO AND FUTURE DIRECTIONS

Introduction

Whole Breast Radiation Therapy (WBRT) is an integral component of breast conserving therapy (BCT), resulting in the improvement of local control and overall survival. Conventional WBRT is a 5-week treatment which is followed by boost to the tumor bed for a week. This 6 weeks treatment may pose a problem for working women or those who stay at long distances from the RT centre. Due to these reasons, even in west only 43% of the eligible women undergo BCT and of those who opt for BCT 14% do not take RT.

Recurrence patterns in early breast cancer have been studied extensively and it has been observed that majority of the local recurrences are at the site of tumor bed only. Only a small percentage of patients recur outside the tumor bed and these recurrences in fact are more like second primaries. Giving radiation to whole breast does not alter the recurrence pattern. Therefore, this concept has evolved for more than a decade ago wherein radiation is considered only to the tumor bed with margin which is termed as partial breast irradiation. Due to reduction in the volume of irradiation, it is possible to give higher dose per fraction thereby reducing the overall treatment time. This entire concept is termed as accelerated partial breast irradiation (APBI).

Methods of APBI

Interstitial brachytherapy (IB): IB is one of the time tested methods of APBI. This involves placement of needles at the site of the tumor bed, either intra-operatively or post-operatively. The needles are replaced by the flexible tubes and radiation is delivered to the tumor bed with 1-2cm margin (Fig 1, Fig 2). Generally the doses given are 34Gy in 10 fractions twice daily. Earlier IB was done using low dose rate brachytherapy (LDR). However, now it has been replaced with high dose rate brachytherapy (HDR) using ¹⁹²Iridium as the source.

Mammosite: Mammosite is a balloon device which is inserted into the tumor bed cavity either, intra-operatively or post-operatively. The diameter of the balloon is decided based on the size of the cavity. The advantage of this technique is simplicity as compared to IB. However,

the dose distribution with this technique is spherical which results in higher dose to the skin and ribs. Recently, MD Anderson Cancer Centre reported data on 92735 women, of which 6952 were treated with brachytherapy and 85783 were treated with WBRT. The data clearly showed increased rate of complications such as infections, breast pain, fat necrosis, rib fracture in women treated with brachytherapy, majority of whom were treated with mammosite. It also resulted in increased rates of mastectomy.

Intra-Operative Devices

Targeted intra-operative therapy (TARGIT): TARGIT is an intra-operative device with 50kv X ray source which is inserted at the time of the surgery and the treatment is delivered intra-operatively. A single fraction dose of 21Gy is delivered at the surface. The advantage of this technique is that the entire treatment is completed in one day. But there have been severe concerns regarding the dose distribution and coverage of the cavity wall. The effective dose at 1cm with this technique is only 5-7Gy.

Intra-operative electrons (ELIOT): This technique was started by Veronesi's group in which immediately after the lumpectomy the tumor bed is exposed and single fraction treatment to a dose of 21Gy is delivered with appropriate energy of electrons. While the advantage of this technique is completion of the treatment at the time of surgery, one of the issues with this technique is coverage of the walls of lumpectomy cavity.



Figure 1: Interstitial Brachytherapy for Accelerated Partial Breast Irradiation



Figure 2: Dose distribution of interstitial Brachytherapy for Accelerated Partial Breast Irradiation

External RT: External RT techniques, such as 3-dimensional conformal RT (3DCRT) and intensity modulated radiation therapy (IMRT), have also been used for APBI. The doses used for these techniques are similar to that of IB. The advantages of these techniques are non-invasive nature of the treatment. But the disadvantage is higher volumes of irradiation resulting in poor cosmetic outcome.

Importance of Patient Selection

Patient selection is one of the most important factors in the success of APBI program. To begin with as per the recommendations given by American Brachytherapy society and American Society of Surgeons, essentially unifocal tumors up to 3 cm with free margins and no extensive intraductal component (EIC) and negative nodes were considered suitable for APBI. However, now American Society for Therapeutic Radiation Oncology (ASTRO) has issued consensus guidelines for APBI outside the clinical trial. According to these guidelines, women over 60 years of age with, tumor size of up to 2 cm, node negative, receptor positive status, are considered suitable for APBI.

Outcome with APBI

One of the largest single institution phase II data is from William Beaumont Hospital where they have treated 199 women with APBI, using IB and comparing with those receiving WBRT. At a median follow up (FU) of > 10 years, 12 year actuarial local recurrence rate (LRR) with IB was only 5% and this was comparable to that of WBRT. Similarly, the Hungarian group has also reported their 12-year LRR of 9.3%. German-Austrian group has recently reported 5 year LRR of 2% with a median FU of 5 years in 274 women. Apart from these series, various other series have shown very impressive local control rates of 94-98%. One of the largest phase II data of mammosite is from Vicini et al (n=1440) where they observed 5-year local control rate of 96.2% at a median FU of 65 months.

Phase III Data: Published and Ongoing Trials

Currently, there are 7 larger randomized trials going on in different parts of the world using various techniques for APBI. The first published data is from the Hungarian group which compared WBRT with IB/electrons in 258 women with T₁N₀₋₁mic where LRR with APBI was 4.7% while with WBRT it was 3.7%. Recently, TARGIT group reported LRR of only 1.2% at 4 years in their randomized trial comparing WBRT with TARGIT device in 2232 women. However, median FU of 2 years for the entire series was one of the major drawbacks of this trial. Unpublished data for ELIOT group which considered IORT in the randomized

trial of 1306 women, clearly showed statistically significant increase in the LRR in women treated with APBI at a median FU of 5 years. Hence, such intra-operative techniques should be used with extreme caution.

Apart from these trials, there are 4 large randomized trials which are ongoing currently. These include NSABP B39 trial in USA, GEC-ESTRO multicentric trial in Europe, IMPORT Low trial in UK and RAPID trial in Canada. After completion of these trials, data of more than 15000 women randomized in various trials will be available and will possibly give conclusive evidence of the APBI as an alternative to WBRT.

Applicability of Western Literature in India

While the currently available data of APBI is very impressive in select groups of patients, its applicability in India is really questionable. Unlike the West, there is no screening for breast cancer in India. Hence, majority of the patients present with larger tumor sizes. In one of the largest data of BCT in India, the median tumor size was 3 cm, the node positivity rate was as high as 39% and 70% of the tumors were grade III. Hence, currently <5% of women with breast cancer in India are suitable for APBI. Therefore investing in new equipments, such as mammosite, IORT and TARGIT appears unreasonable in India. In case if we have to consider APBI, IB is the time tested and easily available modality of treatment for APBI in the Indian scenario.

Indian Experience

One of the largest experience of APBI is from Tata Memorial Hospital where IB has been practiced since 2000. In well selected women (N=250) at a median FU of 64 months, the 5-year local control rates were 95.5% and overall survival was also 95.5%.

Future Directions

APBI is a good alternative modality of treatment to WBRT in select groups of women with early breast cancer. Currently IB appears to be the best modality of treatment for APBI. The use of mammosite and ELIOT technique will show decline in future due to increased rates of complications, mastectomy rates and negative outcome respectively. Long term data of TARGIT device is awaited for any valid conclusions. Number of women suitable for APBI in India is extremely low at present. Till the time results of various multicentric trials are reported with long term outcome, APBI remains as an investigational treatment.

(Dr Ashwini Budrukhar, Associate Professor, Radiation Oncology, Tata Memorial Hospital, Mumbai)

PERSPECTIVE

BREAST CANCER SCREENING WITH IMAGING

The significant decrease in breast cancer mortality, which amounts to nearly 30% since 1990, is a major medical success and is due, in large part, to the earlier detection of breast cancer through mammographic screening. Mammography is the mainstay of screening for clinically occult disease. However, it has well recognized limitations, and recently, other imaging techniques including ultrasound and magnetic resonance imaging (MRI), have been used as adjunctive screening tools, mainly for women who may be at increased risk for the development of breast cancer.

The Society of Breast Imaging, and the Breast Imaging Commission of the American College of Radiology issued recommendations based on available evidence to provide guidance to patients and clinicians on the use of imaging to screen for breast cancer.

Recommendations for Imaging Screening for Breast Cancer by Imaging Techniques**1. Mammography*****i) Age at Which Annual Screening Mammography Should Start:*****Age 40**

- Women at average risk.

Younger Than Age 40

- BRCA1 or BRCA2 gene mutation carriers: by age 30, but not before age 25.
- Women with mothers or sisters with pre-menopausal breast cancer: by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of relative, whichever is later.
- Women with 20% lifetime risk for breast cancer on the basis of family history (both maternal and paternal): yearly, starting by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of the youngest affected relative, whichever is later.
- Women with histories of mantle radiation received between the ages of 10 and 30: beginning 8 years after the radiation therapy but not before age 25.
- Women with biopsy-proven lobular neoplasia, ADH, DCIS, invasive breast cancer, or ovarian cancer regardless of age.

ii) Age at Which Annual Screening with Mammography Should Stop

- When life expectancy is 5 to 7 years on the basis of age or comorbid conditions.
- When abnormal results of screening would not be acted on because of age or comorbid conditions.

2. Ultrasound (in Addition to Mammography)

- Can be considered in high-risk women for whom magnetic resonance imaging (MRI) screening may be appropriate but who cannot have MRI for any reason.
- Can be considered in women with dense breast tissue as an adjunct to mammography.

3. MRI-Breast

- Proven carriers of a deleterious BRCA mutation: annually starting by age 30
- Untested first-degree relatives of proven BRCA mutation carriers: annually starting by age 30
- Women with 20% lifetime risk for breast cancer on the basis of family history annually starting by age 30
- Women with histories of chest irradiation (usually as treatment for Hodgkin's disease) annually starting 8 years after the radiation therapy
- Women with newly diagnosed breast cancer and normal contralateral breast by conventional imaging and physical examination

Single screening MRI of the contralateral breast at the time of diagnosis may be considered in women with between 15% and 20% lifetime risk for breast cancer on the basis of personal history of breast or ovarian cancer or biopsy proven lobular neoplasia or atypical ductal hyperplasia.

Screening with Digital Mammography

Several studies comparing the performance of digital mammography and film-screen techniques for screening have found equivalent sensitivity for breast cancer detection. However, digital mammography performs significantly better than analog mammography in premenopausal and perimenopausal women, aged 50 years, and those with dense breasts. For these women, digital mammography might be preferred.

According to ACR guidelines, description of detected abnormalities and recommendations for subsequent follow-up studies should be included in the report. They must be classified according to final assessment categories defined in the ACR BIRADS (Breast Imaging Reporting and Data System).

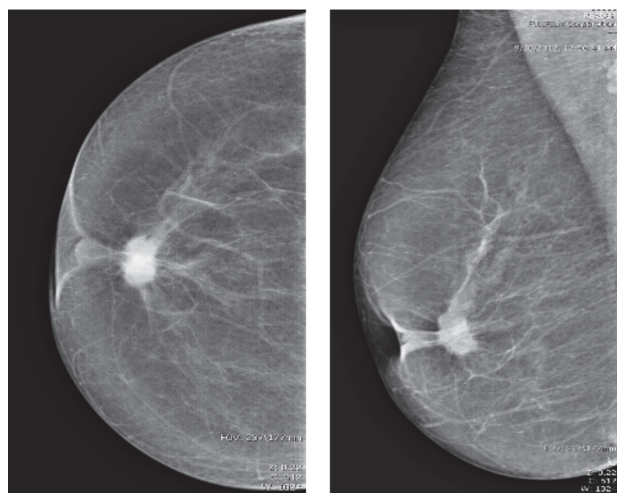


Fig 1: Cranio caudal and MLO view of a digital mammogram showing spiculated retro-areolar region mass with nipple retraction

Screening with Ultrasound

Sensitivity of mammography is lower in women with dense breasts, it has been shown that the use of supplemental ultrasound screening will result in the detection of otherwise occult cancers.

Table: BIRADS Classification as Defined by American College of Radiology

| Mammographic Assessment | BI-RADS® Assessment Category | Description |
|-------------------------|------------------------------|---|
| Incomplete | 0 | Need additional imaging evaluation and/or prior mammograms for comparison |
| Complete | 1 | Negative |
| | 2 | Benign finding(s) |
| | 3 | Probably benign finding: initial short interval follow up suggested |
| | 4 | Suspicious abnormality: biopsy should be considered |
| | 5 | Highly suggestive of malignancy: appropriate action should be taken. |
| | 6 | Known biopsy proven malignancy: appropriate action should be taken |

Screening with Breast MRI

For women with the highest risk for developing breast cancer, screening technologies in addition to mammography have been adopted. These have been particularly sought after for those women at risk for hereditary breast cancer, for which mammographic screening may have relatively low sensitivity. Several

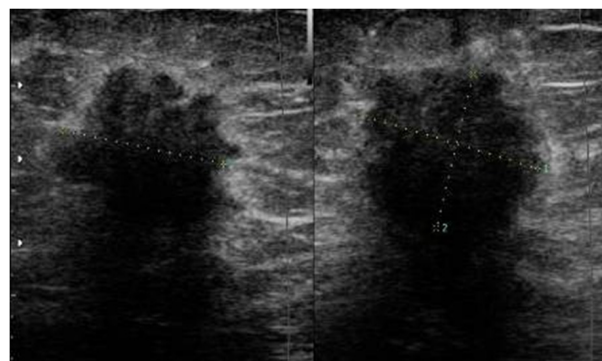


Fig 2: Typical malignant breast mass on USG- irregular hypoechoic nodule with posterior acoustic shadowing.

prospective trials of MRI screening of women at risk for familial breast cancer have shown increased detection of breast cancer with the use of this modality compared to mammographic screening. Regular screening can be done due to absence of radiation in MRI.

For women with newly diagnosed breast cancer, there is evidence that a single round of screening of the contralateral breast with MRI at the time of diagnosis will detect otherwise occult malignancy in approximately 3% to 9% of these women.

It is important to emphasize that breast MRI is not meant to replace mammography. There are cases,

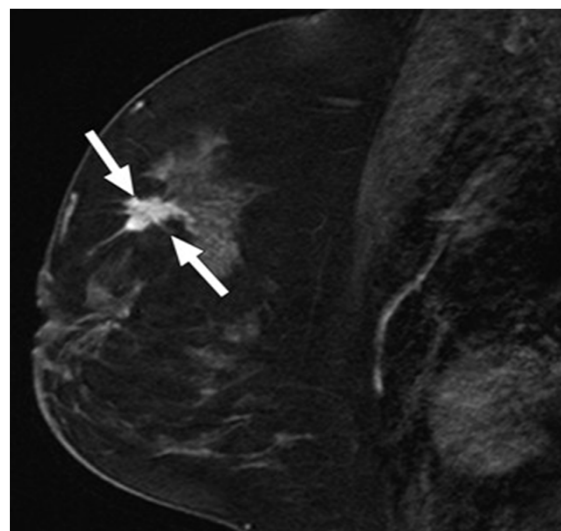


Fig 3: Contrast MRI breast showing a spiculated enhancing lesion in right breast consistent with carcinoma breast

particularly of DCIS (ductal carcinoma in situ), that are detectable by mammography but not by MRI. In performing screening MRI and mammography, they can either be done concurrently or separated by 6 months interval.

(Dr Dibyamohan Hazarika, Consultant, Dept of Radiology and Imaging)

RESEARCH & DEVELOPMENT

CD74 in Triple-Negative Breast Cancer

According to a study conducted at the First Affiliated Hospital of Liaoning Medical College, China, CD74 may be a potential novel target for triple-negative breast cancer (TNBC). Five hundred and eighty breast cancer specimens were enrolled in the study to evaluate the expression status of CD74 in breast cancer stem cells and its clinical implications. CD74 protein was also correlated with the clinicopathological parameters and prognosis. Altogether, 468 (80.69 %) of the 580 breast cases showed CD74-positive expression. On analysis CD74 was observed to be related to lymph node metastasis and TNBC ($P=0.01$ and 0.001). In the Cox regression test, CD74 protein was detected as an independent prognostic factor ($P=0.001$). CD74 was consistently expressed in triple-negative subgroups of breast cancer and, therefore, might be a new potential marker.

(Tumour Biol, Aug 31, 2012)

Early Detection Markers for Breast Cancer

Extensive research is ongoing on circulating miRNAs as promising novel markers for various diseases. A recent study has investigated their potential to serve as minimally invasive, early detection markers for breast cancer in blood plasma. Profiling was done for miRNAs extracted from the plasma of early stage breast cancer patients and healthy control individuals using TaqMan Low Density Arrays. Selected candidates identified in the initial screen were further validated in an extended study cohort of 207 individuals, including 127 sporadic breast cancer cases and 80 healthy controls via RT-qPCR. Four miRNAs (miR-148b, miR-376c, miR-409-3p and miR-801) were shown to be significantly upregulated in the plasma of breast cancer patients. The combination of only three miRNAs (miR-148b, miR-409-3p and miR-801) had an equal discriminatory power between breast cancer cases and healthy controls as all four miRNAs together ($AUC=0.69$) the ROC curve analysis. Based on the results of this study, the identified miRNAs might be of potential use in the development of a multi-marker blood-based test to complement and improve early detection of breast cancer.

(Int J Cancer, Aug 28, 2012)

Landscape of Cancer Genes in Breast Cancer

A team of researchers at the Wellcome Trust Sanger Institute, England, have examined all the genes in the genomes of 100 cases of breast cancer. The mutated cancer-causing genes were different in different cancer samples. They searched for driver mutations in over 21,000 genes to identify new cancer genes that lead to the development of breast cancer and found evidence for nine new cancer genes involved in the development of this cancer. These genome analyses provide a direct survey of the landscape of driver mutations in breast cancer. The team found that driver mutations were present in at least 40 different cancer genes. Most individual cancers had different combinations of mutated cancer genes, demonstrating the substantial genetic diversity in breast cancer. In 28 cases, they found only a single driver and the maximum number of driver mutations in an individual cancer was six. This comprehensive study reveals the full diversity of the driving events that convert normal breast cells into breast cancers.

(Nature, May 16, 2012)

Mammographic Density and Ki-67 in Breast Cancer

Scientists from Germany have analyzed the association between mammographic density (MD) and proliferation marker Ki-67 in invasive breast cancers (BC). In a large case-only study involving 1,975 patients with incident BC, data was available related to the risk factors and hormone receptor expression. MD status was assessed as percentage mammographic density (PMD). Association of the Ki-67 proliferation index and PMD was studied using ANCOVA, with PMD as the target variable and including factors such as age, parity, use of hormone replacement therapy (HRT), and body mass index (BMI). There were no differences in PMD between women with BC who had low and high Ki-67 values. However, significant differences were observed in women with low BMI, and in women using postmenopausal HRT. In these subgroups, the Ki-67 expression index increased with decreasing PMD. PMD also correlated with BMI, parity status, and menopausal status stronger in patients with low proliferating tumors, and with progesterone receptor expression in patients with high proliferating tumors. MD correlates inversely with Ki-67 proliferation in BC tumors only in some subgroups of BC patients, defined by commonly known BC risk factors that are usually associated with MD as well.

(Breast Cancer Res Treat, Aug 31, 2012)

NEW TECHNOLOGIES

New Tool to Predict the Benefit of Radiation

The role of radiation therapy (RT) after conservative surgery (CS) remains controversial for older patients with breast cancer. Guidelines have suggested that RT may be omitted in selected patients with favorable disease. Researchers at MD Anderson Cancer Center, USA, developed a nomogram to predict the likelihood of long-term breast preservation with and without RT by looking at records of 16,092 women aged 66 to 79 who were diagnosed with breast cancer and had lumpectomy between 1992 and 2002. They also recorded the characteristics of the cancer, lymph node status, history of RT as well as mastectomy after recurrence. Median follow-up of 7.2 years. Overall 5 and 10 year mastectomy-free survival (MFS) rates were 98.1% and 95.4% respectively. The nomogram demonstrated good accuracy in predicting MFS, with a bootstrap-corrected concordance index of 0.66. This tool predicts 5 and 10 year MFS among older women with early breast cancer using clinicopathologic factors and can aid clinical decision making by estimating predicted benefit from RT.

(J Clin Oncol, June 25, 2012)

Perjeta for Late-Stage Breast Cancer

The US Food and Drug Administration (FDA) approved Perjeta (pertuzumab, is combine of trastuzumab and docetaxel), a new anti-HER2 therapy, to treat patients with HER2-positive metastatic breast cancer who have not received any prior treatment. The FDA approved Perjeta based on the results of the CLEOPATRA trial which showed that women diagnosed with metastatic, HER2-positive breast cancer who were treated with a combination of Perjeta, Herceptin and Taxotere lived 6 months longer without the cancer progression compared to women treated with Placebo, Herceptin and Taxotere. The most common side effects observed in patients receiving Perjeta in combination with Herceptin and Taxotere were diarrhea, hair loss, neutropenia, nausea, fatigue, rash, and peripheral sensory neuropathy. The therapy was reviewed under the agency's priority review program, which provides for an expedited six-month review of drugs that may offer major advances in treatment.

(The US FDA, June 8, 2012)

Promising Technique for Breast Cancer Screening

X-ray mammography is an important diagnostic tool but has certain drawbacks of false positive and negative results and exposure to low doses of ionizing radiation. Researchers from University of Twente, The Netherlands, used a new imaging device which uses photoacoustics, light-induced sound, rather than ionizing radiation to detect and visualize breast tumors. The study conducted on 12 patients with diagnosed malignancies provide support that the technology can distinguish malignant tissue by providing high-contrast images of tumors. This technology, called optical mammography reveals a clear contrast between blood-vessel dense tumor areas and normal vessel environments. However, it is difficult to target the specific area to be imaged with this approach. By comparing the photoacoustic data with the conventional forms of imaging (like X-ray and MRI) and tissue exams, the researchers showed that malignancies produced a distinct photoacoustic signal that is potentially clinically useful for diagnosing breast cancer. The team also observed that the photoacoustic contrast of the malignant tissue is higher than the contrast provided by the conventional X-ray mammographies. The results, however, need to be further evaluated in a larger group of patients.

(Medical News Today, May 9, 2012)

Sequencing of BRCA Gene Mutations

Scientists from Canada have developed a new Next Generation Sequencing (NGS) approach to provide a more effective method of BRCA1 and BRCA2 mutational analysis. Individuals with mutations in BRCA1/2 genes have a significantly higher risk of developing breast and ovarian cancers. The investigators used long range PCR to generate amplified BRCA1/2 DNA (amplicon) of 12 familial breast cancer patients and screened using NGS, which increases speed and throughput. While conventional screening methods target only the exons of BRCA1/2, NGS can screen the entire genomic region, including introns. The specimens had also analyzed using conventional methods for a comparison. Results illustrate that NGS can provide comprehensive genetic information more quickly, accurately, and at a lower cost than conventional approaches allowing NGS to be a more effective method. Advances in NGS will play an important role in enabling molecular diagnostics and personalized treatment of breast and ovarian cancers.

(Journal of Molecular Diagnostics, Sep 2012)

CLINICAL TRIALS

Anastrozole and Fulvestrant in MBC

Researchers from Irvine Medical Center, USA, conducted a phase III randomized trial to see the effect of anastrozole versus anastrozole and fulvestrant as first line therapy for postmenopausal women, with metastatic breast cancer. Previously untreated patients for metastatic disease were randomly allocated into two groups in a 1:1 ratio. Group one received 1 mg of anastrozole orally every day, and patients of group two received anastrozole and fulvestrant in combination. Fulvestrant was administered intramuscularly at a dose of 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter. The primary end-point was progression-free survival (PFS) and overall survival (OS). The PFS was 13.5 months in group 1 and 15.0 months in group 2. The OS was also longer with combination therapy (median, 41.3 months in group 1 and 47.7 months in group 2). Through this study, it was concluded that the combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant.

(*N Engl J Med*, August 2012)

Docetaxel & Epirubicin for Advanced Breast Cancer

Scientists from Japan conducted a multicenter phase II study in advanced and recurrent breast cancer patients to examine the efficacy and tolerability of docetaxel (DOC) in combination with epirubicin (EPI) as the first-line treatment. A total of 56 female patients not previously treated for metastatic disease were recruited in the study with median age of 53 years. Advanced disease was present in 86% of patients, recurrent disease in 14% and 38% of patients had metastasis at three or more sites. Patients received DOC (60 mg/m²) and EPI (60 mg/m²) on day 1 every 3 weeks and the median number of courses administered was 6. The median dose intensity was 18.7 mg/m²/week for DOC and EPI. Results of the trial showed complete response in 5%, partial response in 54%, and stable disease in 33% of patients, with a disease control rate of 92%. The progression free survival was 78.3%, and the overall survival was 91.9% at 1 year. These results suggest that the DOC and EPI with doses of 60 mg/m² is an active and generally well-tolerated regimen that can be used as first-line chemotherapy for patients with advanced breast cancer.

(*Gan To Kagaku Ryoho*, May 2012)

Electrochemotherapy for Cutaneous Recurrence

According to the results of a phase II trial, electrochemotherapy is a promising treatment alternative for cutaneous recurrences of breast cancer. Cutaneous recurrence causes discomfort due to ulceration, oozing and pain. Seventeen heavily pre-treated patients were recruited in the study and received bleomycin injection followed by application of electric pulses. Primary endpoint was objective response evaluated by clinical examination. Secondary endpoints included response evaluated by PET/CT, change in lung diffusion capacity, patient reported symptoms, and distress related to bodily appearance. Of total patients, twelve were evaluable with follow up of more than 8 weeks. CT showed that four (33%) patients achieved over 50% tumor volume reduction. Clinically complete and partial response was achieved in one (13%) patient. Symptomatic relief included decreasing exudates, odour and bleeding. The only side effect was post-treatment pain and treatment was well tolerated in all the patients. Electrochemotherapy is a localised anticancer treatment using electric pulses to make the cell membranes permeable which enhances uptake of drugs, and kill the tumor cells efficiently.

(*Acta Oncol*, July 2012)

Everolimus & Carboplatin in MBC

An open-label, mono-center phase I study designed to determine the maximum tolerated dose (MTD) of everolimus in combination with carboplatin in taxane and anthracycline pretreated patients with progressive metastatic breast cancer (MBC). Despite advances in the first- and second-line treatment of metastatic breast cancer, there is still need for additional treatment options. Fifteen patients with pre-treated MBC were recruited to the study who received weekly carboplatin and daily oral everolimus at different dose-levels (level I: 2.5 mg; II: 5 mg; III: 7.5 mg; IV: 10 mg). Three patients were assigned to dose-levels I to III, and six to dose-level IV and the maximum planned dose-level IV was selected as the maximum tolerated dose (MTD). Patients received a median of four cycles of treatment. Most frequent grade 3 and 4 toxicities included leukopenia, thrombocytopenia and infection. Of total patients, 21% have partial response, 43% stable disease, and 36% progressive disease. Combining carboplatin and everolimus produce higher activity and it is well-tolerated by heavily pre-treated MBC.

(*Anticancer Res*, August 2012)

WATCH-OUT

Gamma Guided Stereotactic Localization System

A United States Patent no. 8,249,693 was assigned to Kieper; Douglas A. et al of Dilon Technologies, Inc. This invention relates to stereotactic gamma-guided localization system for imaging a suspected cancer and guiding a physician in the removal of tissue samples for biopsy. The gamma-guided localization system includes a three step procedure including localization, correlation, and verification. The localization system includes a gamma camera with a set of slant-hole collimators for producing stereo images of a region of interest. A positioning system including a fiducial marker is placed adjacent to the object to be imaged and held rigidly in place to provide correlation of the location of the region of interest relative to the fiducial marker. A gamma emitting marker is then positioned at the calculated location of the region of interest and imaged to verify that the calculated position corresponds to the actual location. The positioning system can then be used to accurately position and support any other hardware that needs to be positioned at the region of interest.

(www.uspto.gov, Sep 5 2012)

Detecting Mutant FGFR4 in Breast Cancer

European patent no. WO/2012/115068 was awarded to FUTAMI, Takashi et al of Astellas Pharma Inc., Tokyo on 30th August 2012. The present invention describes a novel gene mutation that is a cause of breast cancer, and thereby provide a method of detecting breast cancer in test subjects by detecting the genetic mutation or the protein associated with the genetic mutation; a method of diagnosing breast cancer in test subjects; and a primer set, probe and detection kit thereof. This includes a method for detecting the presence of breast cancer in test subjects which includes a step for detecting the mutation of the 82nd asparagine in the tyrosine kinase domain of fibroblast growth factor receptor 4 (FGFR4) to asparinic acid or lysine in a sample obtained from a test subject.

(patentscope.wipo.int, Aug 08, 2012)

Targets for Breast Cancer Treatment

The importance of cross-talk between a cancer and its microenvironment has been increasingly recognized. A better understanding of this cross-talk would provide

improved methods for diagnosis, prognosis and therapy of cancer. Charis Eng of The Cleveland Clinic Foundation (Cleveland, OH), USA, was awarded the US patent No. 8,206,910 on June 26, 2012. The invention is directed to methods of diagnosing breast cancer, susceptibility to breast cancer, nodal metastasis of a breast cancer and screening for breast cancer in an individual in need thereof comprising detecting the presence of a loss of heterozygosity/allelic imbalance (LOH/AI) at one or more specific loci (markers) in the genome of the individual, wherein the presence of the LOH/AI at one or more specific loci in the genome of the individual is indicative of a diagnosis of breast cancer in the individual. TP53 mutation analysis and genomewide analysis of loss of heterozygosity and allelic imbalance on DNA from isolated neoplastic epithelial and stromal cells from 43 samples of hereditary breast cancer and 175 samples of sporadic breast cancer were performed. Compartment-specific patterns and TP53 mutations were analyzed. Associations between compartment-specific TP53 status, loss of heterozygosity or allelic imbalance, and clinical and pathological characteristics were computed.

(www.freepatentsonline.com, Jul 30, 2012)

Vaccine for the Prevention of Breast Cancer Relapse

United States Patent no. 8,222,214 has been awarded to George E. Peoples, et al. of The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (Rockville, MD) on July 17, 2012. The invention features methods to induce and maintain a protective cytotoxic T-lymphocyte response to a peptide of the HER2/neu oncogene, E75, with the effect of inducing and maintaining protective or therapeutic immunity against breast cancer in a patient in clinical remission. The methods comprise administering to the patient an effective amount of a vaccine composition comprising a pharmaceutically acceptable carrier, an adjuvant such as recombinant human GM-CSF, and the E75 peptide at an optimized dose and schedule. The methods further comprise administering an annual or semi-annual booster vaccine dose due to declining E75-specific T cell immunity. The composition can be administered approximately three to six times or more on a monthly basis until the protective immunity is established. In some aspects, the composition further comprises an adjuvant, such as recombinant human granulocyte macrophage-colony stimulating factor (GM-CSF).

(www.uspto.org, Aug 10, 2012)

GLOBE SCAN

Missing Breast Cancer Genes

Researchers from the University of Adelaide are hoping to better understand why the mutated genes for breast and ovarian cancers are not passed on more frequently from one generation of women to the next. That's despite a documented link between breast cancer genes and increased fertility in women. It is hypothesized that the so-called "grandmother effect" may in part be the reason behind this phenomenon. In an earlier study, researchers found that post-menopausal women create a 'grandmother effect', that is, the longer they live, the more they are able to support their daughters and their grandchildren, thereby creating an environment in which more grandchildren are born. The reverse of this is that women who die earlier, such as from breast or ovarian cancer, which are usually post-menopausal, will no longer be able to support their daughters and grandchildren. This has the effect of limiting the number of grandchildren born, and therefore the chances of passing on the mutated genes from one generation to the next is also limited. However, the "grandmother effect" does not entirely negate the increased fertility caused by breast cancer genes. Our change to today's industrial and technological age has been relatively rapid in human history. For most of our existence, we have been hunter-gatherers. During this time, female fertility is limited, and this may have reduced the increase in fertility caused by mutations of these genes.

(Australia: *Proc Royal Soc B*, May 8, 2012)

Male Breast Cancer

Male breast cancer (MBC) is an uncommon disease and there is limited information on the prognostic impact of routinely used clinicopathological parameters. In a retrospective setting, researchers reviewed 197 MBC patients with accessible paraffin-embedded tumor tissue and clinicopathological data. Immunohistochemical (IHC) stainings were performed on tissue microarrays and histological grading on conventional slides. Estrogen receptor (ER) and progesterone receptor positivity were demonstrated in 93% and 77% of patients, respectively. Nottingham histologic grade (NHG) III was seen in 41% and HER2 positivity in 11%. Classification into molecular subtypes using IHC markers according to three alternative definitions

revealed luminal A and luminal B in 81% vs. 11%; 48% vs. 44% and 41% vs. 42% of cases. No difference in breast cancer death between the luminal subgroups was demonstrated, regardless of definition. Hence MBC tumors were more often of high grade, whereas HER2 overexpression was as frequent as in FBC. Lymph nodes, tumor size and ER status were independent predictors of breast cancer death. The prognostic impact of molecular subtyping in MBC seems to differ from that previously established in FBC.

(Sweden: *Acta Oncol*, Aug 29, 2012)

Metastasis Spread Risk

Cancer research scientists have seen that high levels of molecular modification, called methylation, on a gene called CACNA2D3, were associated with spread of disease in breast cancer patients. The gene CACNA2D3 suppresses tumor genes and prevents cancer. Breast cancer cells are highly methylated and healthy breast cells are not methylated. This study shows that the development of methyl groups on the genes inhibits the protection against cancer development. This research suggests that methyl groups can muffle the messages given by the CACNA2D3 gene, blocking its potential protective effect against breast cancer. Methylation of the gene could be used to flag up breast cancer patients who have a greater chance of the disease spreading, helping doctors decide what treatment plan would be most effective.

(UK: *Br J Cancer*, July 12, 2012)

New Target, New Drug

Many breast cancers depend on hormones, including estrogen or progesterone for their survival and proliferation. New research suggests that the androgen (AR) receptor is an additional hormonal target in many breast cancers. Block AR+ breast cancer's ability to access androgen and you block the cancer's ability to survive. That's what the drug enzalutamide does. Preliminary results are promising and show that androgen receptor blockade may indeed be therapeutic. Targeting androgen receptors may be especially important for patients whose cancers haven't responded to existing treatments that target estrogen or progesterone. The Medivation drug enzalutamide blocks the proliferative power of androgen receptors in breast cancer. This is a possible, new first-line target for breast cancer care.

(USA: *Science Daily*, June 2, 2012)

CANCER CONTROL

Blood Test May Predict Recurrence and Survival

Testing the blood of early stage breast cancer patients for circulating tumor cells (CTCs) may predict their chance for recurrence and survival, according to the researchers from MD Anderson Cancer Center, USA. The study included 302 breast cancer patients with average age of 54 years and Stage I, II and III. A system called Veridex Cell Search was used to detect and measure the CTCs. After following the patients for a median period of 35 months, statistical analysis was carried out to find the relation between CTC measurements and progression-free and overall survival. It was found that the relapse rate of patients detected with at least one CTC was 16% as compared to 3% in patients in whom no CTC was detected. The progression-free survival after 2 years of follow-up was found to be 98% in patients with no CTC, 87% for patients with 1 or more CTCs, 79% for those with 2 or more CTCs and 69% for those with 3 or more CTCs. The study concluded that the presence of one or more CTCs predicted early recurrence and decreased overall survival in chemo-naïve patients with non-metastatic breast cancer and can identify the patients who may require additional treatment.

(Medical News Today, Jun 7, 2012)

Mathematical Patterns Interpret Aggressive Cancer

Researchers at the University of Oslo, Europe, have developed a new method to differentiate between breast cancer patients with high and low risks of dying from the disease. The algorithm makes it easier to plan the best treatment for the patients. The method looks at the changes in genetic material in cancer cells. To identify the complex changes in the genome, the mathematical and statistical methods were used. The researchers found the statistical connection between changes in cancer genomes and the course of disease for 600 Norwegian breast cancer patients over ten years. For each patient, about 240,000 characteristics of the genome in the cancer cells were measured. It was identified that high complexity was clearly linked with an increased risk of dying from the disease. The new algorithm recognizes the area of the genome that has a high number of copies which may be focused for targeted and molecular treatment.

(Science Daily, Aug 23, 2012)

Physical Activity and Breast Cancer Risk

Women who exercise and maintain a healthy weight have a reduced risk of breast cancer even if their exercise is limited to mild recreational physical activity before or after menopause, as per a study conducted at University of North Carolina. The researchers analyzed data from women who participated in the Long Island Breast Cancer Study Project, designed to investigate possible environmental causes of breast cancer. The study involved 1,504 women with breast cancer and 1,555 women without breast cancer between the ages of 20 to 98 years. It was found that women who exercised either during their reproductive or post-menopausal years had a reduced risk of developing breast cancer. Those who worked out 10 to 19 hours per week experienced the greatest benefit, with an almost 30 percent reduced risk of developing the disease. However, looking at the joint effect of physical activity, weight gain and body size; the women who experienced substantial post-menopausal weight gain, regardless their level of activity, had an increased risk of developing breast cancer. The study concluded that the mild physical activity may reduce breast cancer risk, but weight gain can eliminate the beneficial effects.

(www.cancer.gov, Jun 25, 2012)

Sleep Duration Link with Aggressive Breast Cancer

A study conducted at Case Western Reserve University, USA, suggests that shorter duration of sleep has been associated with biologically more aggressive tumors as well as likelihood of cancer recurrence. The patients were recruited at the time of diagnosis and asked about the average sleep duration in last two years. The OncotypeDX test assigns a tumor a recurrence score based on the expression level of a combination of 21 genes. The data from 101 breast cancer patients with available OncotypeDX recurrence scores was analyzed. It was found that OncotypeDX recurrence scores were strongly correlated with average hours of sleep per night before the disease diagnosis whereas fewer hours of sleep were related with a higher recurrence score ($R = -0.30, p = 0.0031$). The correlation was limited to post-menopausal patients only ($R = -0.41, p = 0.0011$ for post-menopausal patients vs $R = -0.05, p = 0.80$ for pre-menopausal patients). The data suggest that sleep may affect carcinogenic pathway(s) specifically involved in the development of post-menopausal breast cancer.

(Breast Cancer Res Treat, Jul 3, 2012)

IN FOCUS

GENOMIC PROFILING IN BREAST CANCER

Breast cancer is a heterogeneous and phenotypically diverse disease. It is composed of several biologic subtypes that have distinct behavior and response to therapy. This heterogeneity was first noted over 100 years ago with the identification that simple removal of the ovaries was therapeutic in some breast cancer patients, but not others. Breast cancer characterization (profiling) has significantly advanced since the turn of the millennium due to the development of sophisticated technologies, such as gene expression arrays, which permit simultaneous measurement of thousands of genes to create a molecular portrait of the tumor.

Molecular Profiling

Molecular profiling, based upon variations in gene expression, has been used to characterize breast cancers beyond the conventional use of grade, histology, and immunohistochemical analysis of hormone receptors and human epidermal growth factor receptor-2 (HER2) overexpression. The resulting taxonomy defines the breast cancer intrinsic subtypes.

Breast Cancer Intrinsic Subtypes

Gene expression studies have identified several distinct breast cancer subtypes. These include three main subtypes of estrogen receptor (ER)-negative tumors, basal-like, human epidermal growth factor receptor-2 (HER2)-enriched, and normal-like; and two subtypes of ER-positive tumors, luminal A and luminal B. A sixth breast cancer subtype, termed claudin-low, has also been defined. These subtypes differ markedly in prognosis and in the therapeutic targets they express.

Luminal subtypes: The name “luminal” derives from similarity in expression between these tumors and the luminal epithelium of the breast; they typically express luminal cytokeratins 8 and 18. These are the most common subtypes, make up the majority of ER-positive breast cancer, and are characterized by expression of ER, PR, and other genes associated with ER activation. Luminal A and luminal B have some important molecular and prognostic distinctions.

Luminal A tumors, which probably make up about 40 percent of all breast cancers, usually have high expression of ER-related genes, low expression of the HER2 cluster

of genes, and low expression of proliferation-related genes. Luminal A tumors carry the best prognosis of all breast cancer subtypes.

The less common (about 20 percent) luminal B tumors have relatively lower (although still present) expression of ER-related genes, variable expression of the HER2 cluster, and higher expression of the proliferation cluster. Luminal B tumors carry a worse prognosis than luminal A tumors. Most luminal B cancers have high recurrence scores as assessed by the 12-gene recurrence score assay, and poor 70-gene prognostic signatures.

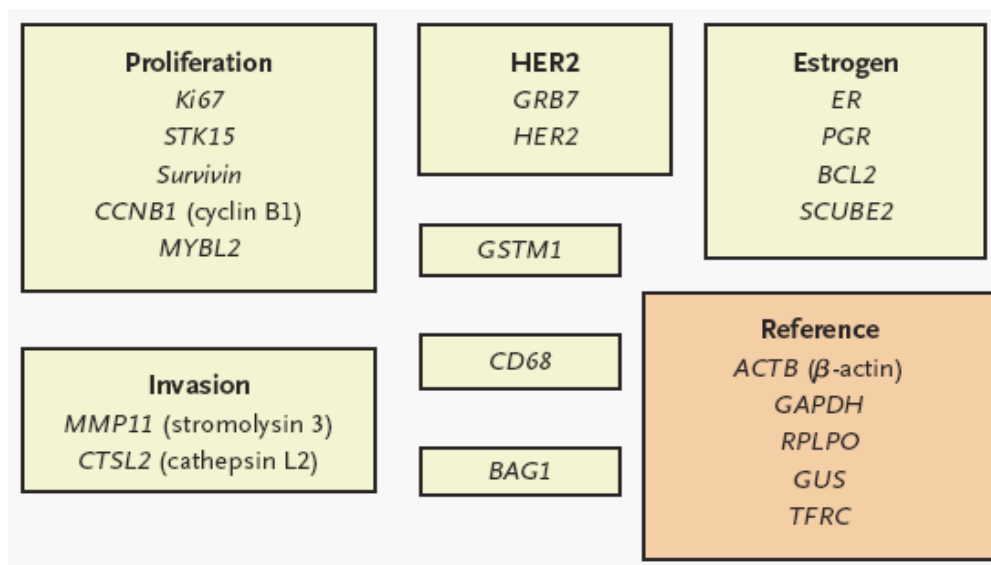
HER2-enriched: The HER2-enriched subtype (previously the HER2+/ER- subtype) makes up about 10 to 15 percent of breast cancers and is characterized by high expression of the HER2 and proliferation gene clusters, and low expression of the luminal cluster. For this reason, these tumors are typically negative for ER and PR, and positive for HER2. It is important to note that this subtype comprises only about half of clinically HER2-positive breast cancer. The other half has high expression of both the HER2 and luminal gene clusters and falls in a luminal subtype. In the era before HER2-targeted therapy, this subtype carried a poor prognosis. This adverse natural history has been markedly affected by therapeutic advances in HER2-directed therapy.

Basal-like: The basal-like subtype, so called because of some similarity in expression to that of the basal epithelial cells, makes up about 15 to 20 percent of breast cancers. It is characterized by low expression of the luminal and HER2 gene clusters. For this reason, these tumors are typically ER-, PR-, and HER2-negative on clinical assays, which has prompted the nickname “triple-negative” to describe them. However, while most triple-negative tumors are basal-like, and most basal-like tumors are triple-negative, there is significant discordance (up to 30 percent) between these two classification methods.

Basal-like tumors have high expression of the proliferation cluster of genes, are virtually always high grade, and evidence widespread genomic instability even early in the disease. They also have high expression of the epidermal growth factor receptor (EGFR), as well as a unique cluster of genes called the basal cluster, which includes basal epithelial cytokeratins 5, 14, and 17.

Prognostic Molecular Profiles

The development of genomics techniques and their ability to simultaneously measure the expression of



Ref: *N Engl J Med* 2005; 352:1605-1607

Figure: Panel of 21 Genes in Oncotype DX Assay

thousands of genes has led to the identification of several biology-based prognosticators, several of which have been validated and are in clinical use. The three most commonly used molecular prognostic profiles are described in more detail below.

Recurrence score: The Oncotype DX test is a 21-gene assay that predicts the patient's likely benefit from chemotherapy and the risk of breast cancer recurrence to inform adjuvant treatment decisions in certain women with early stage invasive breast cancer. The Oncotype DX results are provided in the form of a Recurrence Score™, a number between 0 and 100 which correlates to a specific likelihood of breast cancer recurrence within 10 years of initial diagnosis and benefit of chemotherapy.

The Oncotype DX test has been extensively evaluated in 13 studies with over 4,000 breast cancer patients. These studies include a large validation study published in the *New England Journal of Medicine* and a chemotherapy benefit study published in the *Journal of Clinical Oncology*.

The 21-gene recurrence score (RS, Oncotype Dx®) is among the best-validated prognostic assays, has some value in predicting chemotherapy response, and is relatively unique in that it can be used in fixed tissue. It is recommended by the American Society of Clinical Oncology (ASCO) for use in women with node-negative, estrogen receptor (ER)-positive breast cancer. At this time, there is no role for the RS in hormone receptor-negative breast cancer, and it is likely to be of limited value in HER2-positive breast cancer.

Amsterdam 70-gene profile: The Amsterdam 70-gene prognostic profile (Mammaprint®), one of the first gene expression array-based prognosticators, classifies tumors as low-risk or high-risk for breast cancer recurrence. It requires unfixed, frozen tissue (which must be obtained from the surgical specimen within an hour of surgery and sent in a special container to the company) for DNA microarray analysis of the 70-gene set. The test result, a binary score (low-risk and high-risk), is then derived through an algorithm based upon gene expression.

The 70-gene-profile was developed in a different manner from the 21-gene recurrence score (RS) described above. Investigators from the Netherlands Cancer Institute performed a supervised analysis of gene expression arrays on frozen tissue from primary breast tumors that were used to develop the 70-gene profile. Since the initial publication of the 70-gene prognostic profile, there have been several external validation studies and the score has been found to be an accurate predictive factor.

The Amsterdam 70-gene prognostic profile was the first in-vitro diagnostic multivariate index assay, or IVDMA, to be approved by the US Food and Drug Administration (FDA) in 2007. Although approved for both ER-positive and ER-negative breast cancer, it has limited usefulness in the latter, in whom less than 10 percent have a good 70-gene signature. The other primary obstacle to use of the 70-gene signature is the requirement for frozen tissue, which is not typically obtained. This has significantly limited its uptake despite FDA approval.

Table: Clinical Validation of Mammaprint® (in over 2375 Patients)

| Validation Study | Country | Reference | Year | | | | | |
|--------------------------------------|-----------------|--|------|------|------|------|------|-------|
| | | | 2002 | 2004 | 2006 | 2007 | 2008 | 2009 |
| Mamma Print Discovery | The Netherlands | Van't Vee et al, Nature | 78 | | | | | |
| Primay Validation Study | The Netherlands | Van de Vijver et al, NEJM | | 295 | | | | |
| Independent European study | European Union | Buyse et al, JNCI | | | 302 | | | |
| Dutch patient cohort | The Netherlands | De Mesquita et al, Fur J can | | | 123 | | | |
| Prospective Study | The Netherlands | De mesquita et al, Lancet Oncology | | | | 427 | | |
| Core Needle biopsies | Spain | Mayordomo et al, ESMO Meeting | | | | | 35 | |
| Validation in Older US patients | USA | Wittner et al, Clin Cancer Res | | | | | 100 | |
| Validation in 1-3 LN+ patients | European Union | Mook et al, Breast Cancer Res Treat | | | | | 241 | |
| Postm enopausal patients (>61) | The Netherlands | Mook et al (submitted) / SABCS | | | | | 148 | |
| Patients treated with tamoxifen | The Netherlands | Kok et al, (submitted) | | | | | | 192 |
| German patient cohort | German | Kunz et al, St. Gallen Conference | | | | | | 140 |
| Japenese patient cohort | Japan | Ishitobl et al, Jap Breast Cancer Symp | | | | | | 118 |
| Validation in 4-9 LN+patients | European Union | Saghastchian et al, St. Gallen Conf | | | | | | 167 |
| Neoadjuvant predictive study | The Netherlands | Staver et al, Breast Cancer Res Treat | | | | | | 162 |
| Predictiveness (Meta-analysis) study | USA | Bender et al, ASCO 2009C conference | | | | | | 1,696 |

Source: Agendia Inc

The clinical utility of the 70-gene profile will come from a large international study, the MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial, in which women with node-negative breast cancer undergo clinical risk assessment (using a commonly used online tool, Adjuvant! Online) and the 70-gene signature.

Rotterdam 76-gene signature: The Rotterdam/Veridex 76-gene prognostic signature was developed in a test set of 115 node-negative primary breast cancers from women who did not receive adjuvant therapy and had been followed for more than eight years. Recognizing the genetic heterogeneity of breast cancer, separate prognostic gene sets were developed for ER-negative (ER-, 16 genes) and ER-positive (ER+, 60 genes) disease. The 76 prognostic genes were validated in an independent set of 171 mixed ER+ (75 percent) and ER- (25 percent) tumors, demonstrating 93 percent sensitivity and 48 percent specificity. In multivariate analysis of distant metastasis-free survival, the 76-gene prognostic indicator was independent of clinical variables.

In a subsequent independent validation study in 180 node-negative patients who also did not receive adjuvant systemic therapy, the Rotterdam 76-gene signature was associated with a hazard ratio (HR) of distant relapse within five years of 7.41 (meaning those with a poor signature were over sevenfold more likely to develop distant metastasis than those with a good signature).

As with the 70-gene prognostic profile, clinical use of the 76-gene profile Rotterdam assay is limited by the need for frozen tumor samples.

Summary

Gene expression profiling, a simultaneous analysis of expression of large numbers of genes, has been used to develop breast cancer molecular signatures. These molecular signatures offer the potential for use in clinical practice for prognostic stratification and treatment selection. At present, these molecular prognostic profiles can augment, but do not replace classic clinical factors.

- The 21-gene recurrence score (RS, Oncotype Dx®), among the best-validated prognostic assays, can be used to predict the risk of recurrence in patients with newly diagnosed, node-negative, estrogen receptor (ER)-positive disease and to identify patients who are likely to benefit from chemotherapy added to adjuvant endocrine therapy.
- The Amsterdam 70-gene prognostic profile (Mammaprint®) and the Rotterdam/Veridex 76-gene prognostic signature predict the risk of breast cancer recurrence in patients with node-negative, ER-positive breast cancer.
- The RS can be tested in fixed tumor tissue as opposed to fresh frozen tissue required for the 70-gene and 76-gene profiles.
- These molecular signatures have been developed and tested in patient data sets comprised of younger women, with predominantly ER-positive, node-negative breast cancer and used to predict the risk of early recurrence. Their validity among other patient populations is less certain.

(Dr Ullas Batra, Consultant, Dept of Medical Oncology)

GASTROCON 2012

“GASTROCON 2012”, the 2nd national annual gastro conference was organized by RGCI & RC, Delhi on 25th and 26th August 2012, at Hotel Crowne Plaza, Rohini. The focus was on “Recent advances in HPB malignancies”. It provided latest updates on various aspects of liver, gall-bladder and pancreatic cancers. The program included CME and live endoscopy workshop. It was a great success and was attended by 650 delegates from all over the country and abroad.

The inaugural function was presided over by Mr RK Chopra, Chairman RGCI & RC, Mr DS Negi, CEO, Dr AK Dewan, Medical Director, and organizing secretaries Dr Arvind Khurana, Senior Consultant Gastroenterology; Dr Shivendra Singh, Senior Consultant and Chief, GI Oncosurgery & Liver Transplant.

First session focussed on various aspects of HCC management with lectures from experts, such as Dr SK Sarin, Dr Subhash Gupta, Dr A S Soin, Dr G Chaudhari, Dr S S Bajjal, Dr S K Sharma, Dr AK Chaturvedi and Dr Vineet Talwar. The session concluded with lively panel discussion covering various clinical case scenarios in HCC management.

Second session held on 25th August focused on periampullary and pancreatic cancer with talks from eminent faculty, such as Dr S Shrikhande, Dr SS Sikora, Dr Puneet Dhar, Dr SK Gupta and Dr Swarupa Mitra. Dr S Shrikhande (Head, GI Oncosurgery, TMH Mumbai) gave an excellent talk over how to decrease morbidity associated with Whipple's Pancreaticoduodenectomy and how to decrease mortality in post-operative period. Dr SS Sikora (Head, GI Surgery, Manipal Hospital, Bangaluru) highlighted the role and technique of vascular resection in carcinoma pancreas.

Highlight of the second day of conference was live endoscopic workshop by Dr AK Khurana, Dr Randhir Sud, Dr Malay Sharma, Dr Vikram Bhatia, Dr Vipul Rathore and Dr Rajesh Puri. They demonstrated diagnostic endoscopic ultrasound (EUS), EUS-FNAC, metallic biliary stenting, spyglass cholangioscopy and EUS-guided celiac plexus neurolysis. Dr Vipul Rathore from Endoscopy Asia, Mumbai, and Dr Vikram Bhatia highlighted the role of EUS in diagnosis and treatment of HPB malignancies. Dr Shaesta Mehta from TMH discussed about the epidemiology of gall bladder cancer.



(L to R: Dr Arvind Khurana, Shri DS Negi, Dr AK Dewan, Shri RK Chopra, Dr DC Doval, Dr Shivendra Singh & Dr G Chaudhari)

Last session focused on carcinoma gall bladder and hilar cholangiocarcinoma. The session started with presentation by Dr Shivendra Singh on asymptomatic gall stones. This stimulated lively discussion with the audience, but final conclusion was that at present there is no evidence to support prophylactic cholecystectomy for asymptomatic gall stones. Dr Shivendra showed video on Segment 4b+5 resection for gall bladder cancer, highlighting the technical aspect as well as evidence in support of it as against simple wedge resection of GB fossa. Dr AK Khurana highlighted the palliative treatment options in “Hilar Block”. He discussed both the endoscopic as well as percutaneous modalities in detail. This was followed by lectures by Dr Subodh Varshney, Dr AK Agarwal & Dr DC Doval. Dr Milind Javale, medical oncologist from MD Anderson Cancer Institute gave a keynote lecture on “Gall Bladder Cancer- Lessons Learned from Complex Gall Bladder Cancer”. Conference ended with panel discussion on hilar cholangiocarcinoma moderated by Dr Praveen Sharma. The case capsules were very well formulated and provoked a lot of active participation from the audience.

At the end of the day, it was an extremely gratifying experience for the organizers for having done justice to all the delegates, faculty and sponsors from various parts of India. The scientific content as well as workshop was well applauded by everybody. They all found meeting useful and was able to take away new ideas and pearls of wisdom which will help them to improve the care of patients suffering from HPB cancers.

(Dr Shivendra Singh, Senior Consultant and Chief, GI Oncosurgery & Liver Transplant; Dr Arvind Khurana, Senior Consultant, Gastroenterology)

*Caring Beyond Cure...
Living Beyond Survival ...*

THE PINK RIBBON MEET

-An RGCI & RC Initiative

Event :

Annual Symposium for
Breast Cancer Survivors

Venue :

India International Centre,
Main Auditorium, Lodhi Road,
New Delhi -110 003

Schedule:

Monday, 22nd October 2012

Timing

2.00 p.m. - 5.00 p.m.

Team:

Dr. Kapil Kumar
Dr. Sandeep Mehta
Dr. Ullas Batra
Dr. Veda Padma Priya
Dr. Anjali Kakria
Ms. Talwinder Kaur

Dr. D. C. Doval
Dr. Ashish Goel
Dr. S. K. Sharma
Dr. Kumardeep
Ms. Kiran Anand
Ms. Anita Kumari
Ms. Renu

For registration, please contact :

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**Rajiv Gandhi Cancer Institute
and Research Centre**

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