Breast Cancer: An Overview

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Commonest cancer of women worldwide, with more than one million cases annually

Considerable geographic, ethnic and racial variation in incidence of breast cancer

Affluent populations carry greatest risks, with >80 cases/100,000 populations in a year

Incidence of invasive breast cancer now seems to leveling off in western countries, but increasing in developing nations, due to more urbanization and lifestyle factors
Epidemiology

- Since 1990, age-adjusted mortality from breast cancer coming down, at 2.3% per year

- Decline in mortality due to *early detection, increased awareness and tremendous advances in the multimodal treatment strategy*

- In India, age-adjusted incidence much lower compared to western countries, but an increasing trend visible in large metros and age of onset also appears to be younger
Incidence of Breast cancer in India

Fig. 6.14: Comparison of Age Adjusted Incidence Rates (AARs) Across All PBCRs

BREAST (C50) - FEMALES

- Chennai: 29.3
- Delhi: 29.2
- Mumbai: 27.5
- Bangalore: 27.6
- Aizawl District: 26.0
- Kamrup Urban District: 24.3
- Bhopal: 22.1
- Mizoram State: 18.7
- Sikkim State: 13.9
- Imphal West District: 12.5
- Dibrugarh District: 11.7
- Silchar Town: 11.6
- Mizoram St. (Excl. Aizawl Dt.): 11.3
- Barauni: 9.7
- Ahmedabad: 7.6

Rate per 100,000
Established Risk Factors

**DIET AND DIET-RELATED FACTORS**
- Increased weight (postmenopause) \(\uparrow\)
- Increased height \(\uparrow\)
- Western diet \(\uparrow\)
- High intake of fibre? \(\downarrow\)
- Alcohol \(\uparrow\)
- High intake of fresh fruit and vegetables \(\downarrow\)

**IONIZING RADIATION**
- at times of breast development \(\uparrow\)

**HORMONES AND REPRODUCTIVE FACTORS**
- Young age at menarche \(\uparrow\)
- Regular, ovular menstrual cycle \(\uparrow\)
- Older age at first full-term birth \(\uparrow\)
- Nulliparity \(\uparrow\)
- Older age at menopause \(\uparrow\)
- Oral contraceptives \(\uparrow\)
- Infertility \(\uparrow\)
- Lack of breast feeding \(\uparrow\)

**FAMILY HISTORY OF BREAST CANCER** \(\uparrow\)
- including \(BRCA1, BRCA2, and p53\) germline mutations

**BENIGN BREAST DISEASE** \(\uparrow\)
- including atypical ductal hyperplasia
Gail’s Model for risk prediction

- A model for predicting an individual’s annual and lifetime risks of breast cancer

- Based on patient’s age, no. of first degree relatives with Ca breast, age at first childbirth, age at menarche, no. of breast biopsies and h/o atypical ductal hyperplasia

- Use of exogenous hormones and many other risk factors *not* incorporated in this model
Prevention of Breast Cancer

A) **NSABP-P1 Trial**: Tamoxifen vs Placebo
   1) 5 yrs of Tamoxifen use reduces risk by 50%
   2) Benefit in all age groups
   3) Women with LCIS had 56% reduction of risk
   4) Selectively reduced ER+ve tumours
   5) Major toxicities: Endometrial Ca and TE events

B) **STAR Trial (1999-05)**: Tamoxifen vs Raloxifene
   Risk reduction similar, but less toxicity with Raloxifene, and restricted to women > 50 yrs

C) **Prophylactic Bilateral Mastectomy**: 90% risk reduction in women with family history

D) **Prophylactic Bilateral Oophorectomy**: Reduces risk of both Ca Breast and Ovary in women with BRCA1 and BRCA2 mutations
Genetic Screening

- Only 5-10% of breast cancer patients have germline mutations, showing an autosomal dominant inheritance pattern in familial cancer.

- BRCA1, BRCA2 and p53 genes are affected mainly, of which the first two matter mostly.

- In women with BRCA1 and BRCA2 mutation, lifetime risk of breast cancer 65-75%.

- No definite screening recommendations in those with proved germline mutations.

- ASCO advises annual mammography, clinical, and self-breast exam starting at 25-35 yrs.
Diagnosis and Work-up

- History and Physical Examination
- FNAC/ Biopsy (guided by PE/ USG/Mammo)
- Radiologic Studies: Chest X-ray
  - Bilateral Mammogram
  - Ultrasound/CT abdomen
  (In advanced cases)
  - Bone Scan (st II onwards)
- Laboratory studies: CBC, LFT etc
- Pathological studies: ER/PR/HER2 neu status
  - BRCA in selected cases
Imaging in Breast Cancer Diagnosis and Work-up

**Mammography:**
- Most critical component in imaging of breast cancer
- Bilateral Mammograms a routine work-up procedure
- Typically seen as an ill-defined mass with spiculated margins with or without micro-calcifications
- Useful both as diagnostic and screening procedure
- Average sensitivity 90% and specificity 94%
- Positive predictive value about 10-14% for screened pts, but significantly higher for symptomatic pts
- After mammography guided FNAC/Biopsy, detection rate of malignancy about 30%
Other Imaging tools in Breast Cancer

A) **Ultrasound:**
   1) Useful tool to complement mammography in diagnosis and treatment
   2) As a guide for interventional procedures
   3) Evaluation of lumpectomy cavity site for planning RT boost

B) **MRI of Breast:**
   1) Not used routinely
   2) Supplements mammography and ultrasound in diagnosis of doubtful lesions
   3) Assessment of response after Neo-adjuvant CT
Imaging in Breast Cancer

C) CT Scan: 1) No role in routine work-up and staging
               2) May be done in advanced and node positive cases as a supplement

D) Bone Scan:
   1) Limited value in stage I and II and should be reserved for those with bone pain only
   2) Routine procedure in advanced cases however

E) Pet Scan
   1) No established role in early stage disease
   2) Increasing role in locally advanced, recurrent and metastatic cancers
Breast Conservation Strategy in the Management of Breast Cancer

Why Breast Conservation?

Because the patients want it.
# Conservative Surgery + RT vs Mastectomy

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Comparison</th>
<th>No.</th>
<th>Recurrence</th>
<th>Surv.</th>
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<td>Veronesi et al</td>
<td>Halstead vs quadrant</td>
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<td>(QUART)</td>
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<td>Sarrazin et al</td>
<td>MRM vs WLE + RT</td>
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<td>Fisher et al</td>
<td>MRM vs Lumpectomy</td>
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<td>(NSABP)</td>
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<td>Donegan et al</td>
<td>MRM vs WE + RT</td>
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<tr>
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# Trials of Cons. Surgery with and without Radiotherapy

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<td>(MILAN III)</td>
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<td>Upsala 90</td>
<td>Segmental Resection + RT vs SR Only</td>
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<td>(Sweeden)</td>
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<td>Stewart 89</td>
<td>Lumpectomy + RT vs Lumpectomy only</td>
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<td>(Scottish Trial)</td>
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<td>NSABP 06</td>
<td>Lumpectomy + RT vs Lumpectomy only</td>
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Conclusions from Randomized Trials

- Conservative surgery produces equivalent results as Mastectomy

- Local control will definitely be less if radiotherapy is not added, but survival not influenced

NSABP long term follow-up results prove the point
NSABP-06 12 Year Follow up: Recurrences

Is RT required in all patients after lumpectomy?

Better Local Control Vs Survival

- The improved local control resulting from adjuvant RT after BCS did not translate into improved survival at 20 years.

- The probable reason is long term cardiotoxicity caused by irradiation of the heart in left sided breast cancers.

- Subset analysis of Right versus Left sided breast cancers show left sided RT compromising long term survival at 20 Years.
Local Control vs Survival

Oxford Meta-analysis and Danish Trials infuse fresh data

↓

Firmly establishes the role of loco-regional treatment

To enhance the survival as well
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

EBCTCG Lancet 2005; 366: 2087-2106
Effect of radiotherapy after breast-conserving surgery (10 trials of BCS ± RT) on local recurrence and on breast cancer mortality

6097 women with node-negative disease
Effect of radiotherapy after breast-conserving surgery (10 trials of BCS ± RT) on local recurrence and on breast cancer mortality

1214 women with node-positive disease

5-y gain 30.1% (SE 2.8)

BCS

5-y gain 7.1% (SE 3.6)

BCS+RT

Breast cancer mortality

Logrank 2p = 0.01
Conclusions

- In early breast cancer, local treatments have little impact on breast cancer mortality during the first few years, but have definite, although moderate, effects by 15 years.

- Avoidance of local recurrence in a conserved breast and elsewhere are of comparable relevance to 15 year breast cancer mortality.

- About one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided.
Further development: APBI

Accelerated Partial Breast Irradiation (APBI)

RT to the Tumour bearing area or the affected Quadrant instead of whole breast

As the recurrences occur mostly in the vicinity of the primary tumour

Early results are encouraging
Current Indications for APBI
ABS 2002

- be appropriate candidates for standard BCT
- be \( \geq \) 45 years old
- have invasive ductal carcinoma, unifocal
- have tumour size \( \leq 3 \) cm
- have negative microscopic surgical margins
- be axillary node-negative by axillary dissection (Level I–II) or sentinel lymph node evaluation
Evolution of Adjuvant Drug Therapy in Breast Cancer:

Started with the trial of Ovarian ablation (Cole 1970)

Followed by NSABP and Historic Milan Trial
By CMF

Guided our policy of Adjuvant Therapy till the publication of Meta-analysis few years back
Results of Oxford Meta-analysis

- Recurrence:
  - Control: 53.5%
  - Polychemotherapy: 41.1%
  - 15-y gain: 12.3% (SE 1.6)
  - Logrank 2p < 0.00001

- Breast cancer mortality:
  - Control: 42.4%
  - Polychemotherapy: 32.4%
  - 15-y gain: 10.0% (SE 1.6)
  - Logrank 2p < 0.00001
NIH Consensus on Adjuvant drug therapy

- Adjuvant polychemotherapy should be given to majority of women with localised breast cancer >1 cm. size, regardless of nodal, menopausal or hormone receptor status.

- For women with node negative breast cancer <1 cm., decision to use chemotherapy should be individualised.

- Anthracycline based chemotherapy significantly more effective than CMF (small benefit).
Newer Developments: Role of Taxanes in Adjuvant Treatment

- Both RFS and OS improved significantly with addition or substitution with Paclitaxel or Docetaxel (CALGB 9344, BCIRG)
- Several other studies showed increased RFS only whereas OS improvement not significant (NSABP B28, MDACC 2002)
- Strongest support is for 4 AC→4 T (CALGB) Or 6 cycles of TAC (BCIRG)
- Support use of taxanes in Node positive women, but effect independent of ER Status
Use of Taxanes: Ongoing debate

New data presented at ASCO 2008:
Summary of Recent pooled analysis of 22903 women participating in 13 adjuvant Taxane studies:

- Overall benefits with taxane containing regimes
- Absolute 5 yr risk reduction 5% for DFS and 3% OS
- Not affected by type of Taxane (Pacli or Docetaxel)
- Not affected by Nodal Status (1-3 vs >=4 nodes)
- Independent of ER Status
- Several unresolved issues (cost-benefit analysis and quality of life issues not reported)
- Next Oxford Meta-analysis to provide further insights
Benefits of Endocrine Therapy as Adjuvant Treatment

![Graph A](image1.png)

- **Recurrence Rates**
  - Control: 45.0%
  - Tamoxifen: 33.2%
  - Approximately 5 years

- **Breast Cancer Mortality**
  - Control: 34.8%
  - Tamoxifen: 25.6%
  - Approximately 5 years

- **Analysis**
  - Logrank 2p < 0.0001

![Graph B](image2.png)
Advances in Endocrine Therapy

The 3rd generation Aromatase Inhibitors are an exciting new development in the endocrine therapy of ER+ Breast Cancer in post-menopausal women

- Anastrozole superior to Tamoxifen in reducing the risk of relapse, Survival not affected significantly
- *In advanced breast cancer* in post-menopausal women, Letrozole clearly better, and Anastrozole as good as Tamoxifen.
- No sig. difference in mortality with 5 yrs vs 10 yrs of tamoxifen but recurrence significantly lower in long arm (ATLAS Study)
Targeted Therapy in Breast Cancer

- Transtuzumab (Herceptin), the new symbol of success after Tamoxifen in HER-2 +ve (IHC3 or Fish+) tumours

- Benefits pts with HER2+ve metastatic breast cancers, when combined with chemotherapy or Hormones

- As adjuvant treatment highly consistent results showing improvements in DFS and even OS (HERA, BCIRG and 3 other randomized trials)
Advances in targeted therapy

- Herceptin given for 1 year following completion of primary treatment is a new standard in HER2 overexpressing tumours

- Lapatinib (a dual kinase inhibitor) and Bevacizumab (targeting VEGF) are new promising molecules under clinical evaluation

- Cost-effectiveness analysis needs to be done in our setting, as the absolute benefit (in reducing recurrence) after 1 yr of adjuvant therapy is only 5.5%
Thank You