

The first WHO guidelines development meeting for breast, esophageal and epithelial ovarian cancer was hosted by Tata Memorial Hospital on 7th and 8th October. The breast meeting was held in Prof. Rustom Choksi Auditorium, Tata Memorial Hospital on Saturday 7th October 2006. The faculty members for the meeting were-

Tata Memorial Hospital Breast Cancer Working Group –

Surgical Oncology –	Dr RA Badwe Dr V Parmar Dr MS Nadkarni
Radiation Oncology –	Dr KA Dinshaw Dr Rajiv Sarin Dr Rakesh Jalali Dr Ashwini Budrukkar Dr Anusheel Munshi
Medical Oncology –	Dr Reena Nair Dr Sudeep Gupta Dr Ashish Bakshi
Pathology –	Dr RF Chinoy Dr SB Desai Dr TM Shet
Radiodiagnosis –	Dr MH Thakur Dr SK Ramani

Invited Faculty Members were

Surgical Oncology –	Dr I Mitra, Director, BMHRC, Bhopal Dr Gaurav Agarwal, SGPGI, Lucknow Dr Hemanth Raj, Apollo Hospital, Chennai Dr SVS Deo, AIIMS, New Delhi Dr Sandeep Kumar, Lucknow (could not attend)
Radiation Oncology –	Dr Faith Rangad V, CMC, Vellore Dr B Rajan, RCC, Trivandrum (could not attend) Dr Subodh Pande, BMCH, Jaipur Dr GK Rath, IRCH, AIIMS, New Delhi
Medical Oncology –	Dr PP Bapsy, Kidwai, Bangalore(could not attend) Dr D Raghunadharao, Nizam's Institute, Hyderabad
Pathology –	Dr Madhumati Goel, KGMC, Lucknow

International experts

Pathology -	Dr Marc van de Vijver, Pathologist, Netherlands Dr James Reuben, MD Anderson Cancer Center, Texas, USA
--------------------	--

Practice of evidence based medicine offers the best available care to patients and consistent job satisfaction to the physician and care giver. The breast group at Tata Memorial hospital has evolved Evidence based guidelines for breast cancer in 1999. Having implemented them in clinic for 3 years, these were updated during the Evidence Based Management (EBM) meeting. The EBM meeting was structured to examine collated evidence on focused clinical questions and look at its applicability in Indian urban, semi-urban and rural context. The evidence on robustness of evidence and its applicability formed the basis of EB guidelines for management and referral. The aim of present exercise is to refine the evidence based guidelines for the management of breast cancer across India where there is a gross disparity in the facilities and expertise for cancer treatment depending upon the geographic location of the treating hospital. In other words offer the best evidence based options for care to clinicians and guide health care providers in planning infrastructure facilities to suite primary to tertiary level of care.

In order to facilitate the above aim we first defined three distinct levels of health-care facilities depending upon the availability of infrastructure, the availability of expert clinical care, socioeconomic factors. These levels are

1. Healthcare centers with Minimal Facilities
2. Healthcare centers with Optimal Facilities
3. Healthcare centers with Optional Facilities

The details are as follows –

	MINIMAL	OPTIMAL	OPTIONAL
Surgical Oncology	1. General Surgeon available	1. Surgical Oncologist preferable (by degree or atleast 3 yrs. Training at the best national cancer centre	1. Surgical Oncologist mandatory and provision for super specialty
Medical Oncology	1. Medical oncologist unavailable	1. Medical Oncologist preferable	1. Medical oncologist mandatory 2. Expertise for neutropenia management 3. Bone Marrow Transplant – not mandatory
Radiation Oncology	1. Telecobalt machine available 2. If not, definite access to above available	1. Linear accelerator (6 MV) 2. Multiple energy electrons or brachytherapy 3. Simulator (Conv/CT) 4. External radiotherapy planning system	1. APBI equipment and planning 2. Dual energy LA 3. Brachytherapy planning system 4. Conformal techniques e.g. IMRT, IGRT
Pathology	1. Fine Needle Aspiration Cytology reporting available 2. Basic histopathology reporting mandatory (Details in Appendix) 3. Access to Immuno-histochemistry	1. Fine Needle Aspiration Cytology reporting available 2. Basic histopathology reporting available 3. ER, PgR reporting using immuno-histochemistry available 4. cerb B2 reporting – not mandatory	1. Fine Needle Aspiration Cytology reporting available 2. Basic histopathology reporting available 3. ER, PgR reporting using immuno-histochemistry available 4. Her-2/neu – FISH available
Radiology	1. Mammography facility unavailable	1. Film-screen mammography available	1. Full-field digital mammography available 2. Breast US/MRI available

Clinical Work-up –

The entire panel of experts unanimously agreed that in addition to a detailed clinical history of the patient it was mandatory that the following be incorporated in to the standard case history recording format irrespective of the level of the health care centre –

1. Menopausal status
2. History suggestive of metastatic disease (with leading questions if required)
3. Detailed history of pre-existing co-morbidities.
4. A detailed family history should also be recorded especially if there was a cancer genetics clinic within the health care centre.

Diagnostic and Staging Procedures –

Clinical Staging needs to be accurate, uniform and reproducible. At all levels it is mandatory to perform tumour measurements using at least a six-inch scale (ruler). A careful clinical examination of the axilla and the supraclavicular fossa is mandatory. The same should be repeated on the opposite side. In tumours over 5 cms in diameter and locally advanced disease a detailed metastatic work-up is mandatory to look for metastatic disease in liver, lungs and bones.

In Minimal Centres this should be done with

1. X-ray Chest PA View
2. Ultrasonography of the abdomen and pelvis
3. Liver Function tests (including serum alkaline phosphatase)
4. Symptom directed skeletal radiographs

Optimal Centres need to possess facilities for Computerised Tomography (CT) Scan that would be used to screen for lung and liver metastases and Isotope Bone Scan for screening bone metastases. The availability of Positron Emission Tomography (PET) Scan or PET-CT Scan and MRI facilities would be limited to Optional centres.

At the end of clinical examination and metastatic work-up, if indicated, clinical stage should be reported in the standard TNM classification e.g. cT2 N1.M0 etc. in Minimal Centres a treatment based staging could also be adopted for ease of management e.g.

1. Operable Breast Cancer (OBC) – cT1,T2 N0,N1 M0 (Surgery first)
2. Large operable Breast Cancer (LOBC) – cT3 N0,N1 M0 (Surgery first or neo-adjuvant therapy if the patient wishes breast conservation)
3. Locally Advanced Breast Cancer (LABC) – cT4 any N M0 or any cT N2/N3 M0 (Neoadjuvant treatment mandatory)
4. Metastatic Breast Cancer (MBC) – any T any N M1 – (Palliative treatment without curative intent)

Histopathological Diagnostic Procedures –

Histopathological diagnosis prior to commencement of any therapy is mandatory. In cases where upfront surgery is contemplated in a Centre of any level a Fine Needle Aspiration Cytology (FNAC) should be performed. In equivocal results following a FNAC an incision biopsy can also be performed. If there is overwhelming clinical suspicion of malignancy an excision biopsy is the best method of confirming diagnosis. In patients where neoadjuvant therapy is recommended an Incision Biopsy through an appropriately placed incision is mandatory prior to starting the treatment. Core biopsy and Image guided biopsy should be available at Optimal Centres and Stereotactic Biopsy techniques may be available at Optional Centres.

Breast Imaging –

Minimal Centres should be allowed to treat patients without breast imaging. It is recommended that these centres limit their surgery to modified radical mastectomy only. Patients suitable and keen to conserve their breasts should be referred to Optimal/optional centres. Film-screen mammography is a must for Optimal Centres that would offer breast conservation to suitable patients. Optional Centres should be equipped with full field digital Mammography, USG and MRI Breast for use and should establish their indications in Indian context.

Neoadjuvant Therapy –

Minimal Centres should offer standard C₅₀₀A₅₀F₅₀₀ chemotherapy in a neoadjuvant setting to patients who are chemotherapy naïve. The recommendation is to give at least 4cycles of chemotherapy every 3 weeks or till maximum response is achieved. Since neoadjuvant hormonal therapy requires more precise clinical judgment to evaluate clinical response, it is recommended that practice of neoadjuvant hormonal treatment be restricted to Optimal and Optional Centres. In Optimal Centres, physicians should have the option to decide between C₅₀₀E₁₀₀F₅₀₀ or Taxane-based chemotherapy as standard of care in a neoadjuvant setting. If a post-menopausal patient is unfit for chemotherapy or refuses the same, hormonal therapy in the form of Letrozole/tamoxifen may be offered to hormone receptor positive patients. The use of biological therapy e.g. trastuzumab in the neoadjuvant setting should be restricted to Optional Centres

Surgery –

As Minimal Centres would not possess mammography facilities, it is recommended that these centres practice modified radical mastectomy (see appendix) as standard of care. It is recommended that breast conservation be practiced only if mammography assistance is available. Hence Optimal and Optional Centres must offer breast conservation to interested and suitable cases as part of standard treatment protocols. It is mandatory for all surgeons to orient breast conservation specimens in the standard fashion for accuracy in reporting margins. Partial breast reconstruction using pedicled flaps (*Latissimus Dorsi* or *Transverse Rectus Abdominis Myocutaneous (TRAM)*) or whole breast reconstruction

using breast implants or microvascular free tissue transfer (*Free TRAM, Superior Gluteal Artery Perforator (SGAP) or Antero-Lateral Thigh (ALT) Flap*) should be limited to Optional Centres with an experienced fully trained Plastic Surgery Unit.

Pending the availability of robust evidence to support their use, conservative axillary dissection procedures such as Sentinel Node Biopsy and Axillary Sampling are best performed at Optional Centres. At Minimal and Optimal Centres, it is recommended that surgeons perform a complete axillary dissection with all three levels of nodes being dissected out.(appendix).

Histopathology Report –

A histopathology report in a Minimal Centre must mention the following details – tumour size (in three dimensions), tumour type, tumour grade, status of skin (whether involved microscopically by disease or not), the total number of axillary nodes dissected (at least 10 lymph nodes should be looked for) and the number of lymph nodes affected by cancer. It is mandatory to have access to ER and PgR reporting. Optimal Centres must have facilities for ER and PgR reporting by IHC. In addition to the above, Optimal Centres should also have expertise to report on presence or absence of DCIS, presence/absence of extensive in-situ cancer, status of resection margins (in lumpectomy specimens) and presence/absence of lymphovascular invasion or embolization. Optional Centres must report on presence/absence of perineural infiltration, perinodal extension and status of the adjacent breast. cerb B2 or Her-2/neu reporting by IHC or Fluorescence In-Situ Hybridization (FISH) is mandatory in optional Centres. (See Addendum)

Adjuvant Chemotherapy –

The recommended adjuvant chemotherapy regimens for Minimal Centres are C₅₀₀A₅₀F₅₀₀ x 6 cycles, A₆₀C₆₀₀ x 4 cycles, E C₆₀₀ x 4 cycles; each cycle administered 3 weeks after the previous one after monitoring blood counts. To be able to use anthracycline based regimens it is mandatory that treating centres possess or at least have access to base line cardiac evaluation using 2D-Echocardiography. In the event that baseline cardiac evaluation is not feasible or the patient is unfit for anthracyclines, the recommended regimen is C₅₀₀M₅₀F₅₀₀ (D1 D8 regimen). In Optimal and Optional Centres the choice of chemotherapy should be between six cycles of C₅₀₀E₁₀₀F₅₀₀ or taxane-based chemotherapy (with GMCSF support). Use of biological therapy e.g. trastuzumab should be limited to Optional Centres due the higher costs, greater intensity and higher cardiac side-effects associated with their use.

Adjuvant Radiation Therapy –

Minimal centers would only have cobalt machine or access to such facility and these centers should treat only post mastectomy chest wall/drainage area. It is recommended that radiotherapy for breast conservation be done only at centers with optimal facilities which have a linear accelerator(6MV) and radiotherapy simulator. All

these patients should be treated by whole breast radiotherapy followed by a boost to the tumour bed with margins. Therefore, these centers should also have the facility for electrons or brachytherapy for delivery of boost besides having a proper external radiotherapy planning system.

In centers with optional facilities, modalities which are not yet fully established or standardized such as accelerated partial breast irradiation (APBI) and conformal techniques such as intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT) should be considered.

Adjuvant Hormone Therapy –

Patients with ER and/or PgR receptor positivity must be treated using some form of hormonal manipulation. This hormonal therapy is recommended for a period of at least 5 YEARS after commencement. The hormonal therapy should NEVER be administered concurrently with chemotherapy and should be started only after chemotherapy is completed or stopped. In Minimal Centres eligible patients should receive sequential (after chemotherapy) Tamoxifen 20 mg OD for 5 years or till disease progression. Pre-menopausal patients with hormone sensitive tumors who refuse chemotherapy for any reason might be given the option of bilateral oophorectomy if they are over 40 years of age. In Optimal and Optional Centres premenopausal women should receive five years of Tamoxifen 20 mg OD followed by 2 years of Letrozole 2.5 mg OD (if they are post menopausal by then). The standard recommendation for post menopausal women is 5 years of Aromatase inhibitors either Anastrozole 1mg OD or Letrozole 2.5 mg OD along with calcium and Vit D supplementation and prophylactic use of oral bisphosphonates. The use of reversible ovarian suppression using GnRH analogues (goserelin or leuprolide acetate for 2-3 years) in premenopausal women should be limited to Optional Centres only. Tamoxifen at the dose of 20 mg per day for 5 years continues to be an acceptable choice of adjuvant hormonal therapy for all hormone receptor positive women at any center

Follow Up Protocol

Irrespective of the level of health care centre follow up visits should be as under

6 monthly – Years 0-5

Yearly – Years 6-10

2 yearly – thereafter

At every follow-up visit, thorough clinical examination is recommended coupled with yearly or 18 monthly mammograms. Metastatic work up is not recommended at each follow-up visit unless the patient has symptoms suggestive of disease recurrence.

Metastatic Breast Cancer

The recommendations for management of Metastatic Breast Cancer are tabulated as under

MINIMAL	OPTIMAL	OPTIONAL
Bone metastasis		
<ul style="list-style-type: none"> -Pain Relief -Local RT (symptomatic or wt. bearing regions) or Access to RT -Bisphosphonates -Hormonal therapy* 	<ul style="list-style-type: none"> - Hemibody irradiation 	<ul style="list-style-type: none"> - Hemibody irradiation -Surgical fixation -Vertebroplasty -Trastuzumab for CerbB2 positive patients
Brain metastasis		
<ul style="list-style-type: none"> -Steroids -Whole brain RT or Access to RT -Solitary isolated brain metastasis – refer to optimal centre 	<ul style="list-style-type: none"> - Surgery (if solitary metastasis and at an accessible site and no extracranial disease) + RT 	<ul style="list-style-type: none"> -Whole brain RT with stereotactic boost in appropriate situations OR -Stereotactic radiosurgery

MINIMAL	OPTIMAL	OPTIONAL
Pulmonary/ Pleural metastasis		
<ul style="list-style-type: none"> -Best supportive care -Appropriate systemic therapy -Pleurocentesis 	<ul style="list-style-type: none"> -ICD insertion & pleurodesis 	<ul style="list-style-type: none"> -Second/Third line chemotherapy -Trastuzumab for CerbB2 positive patients
Hepatic metastasis		
<ul style="list-style-type: none"> -Best supportive care -Appropriate systemic therapy 	-	<ul style="list-style-type: none"> -Second/Third line chemotherapy -Trastuzumab for CerbB2 positive patients - Aggressive local therapy for solitary liver metastasis

APPENDIX for HISTOPATHOLOGY

Histopathology report

1. 'T' size of invasive tumour

Appendix - Guidelines for 'T' size measurement –

- Measure & document all three dimensions, but the single greatest dimension is used for T staging.
 - In irregular tumors or tumors which are EIC positive, the gross measurement of the invasive component must be measured with the microscope scale. The final correct measurement may be at divergence from the original measurement but the one done with microscopy must be accepted finally.
 - Measure only the invasive component. However if there are multiple lesions, the size of largest mass is taken as the T size.
 - If there are two different discrete tumors separated by a gap of 2 cm or more, record the sizes of both separately. However the dimension of the single largest tumour is considered for T staging
2. Diagnosis/ Tumor type e.g. Infiltrating duct carcinoma (NOS), infiltrating lobular carcinoma etc
3. Grading as per the Nottingham's (Elston's) modification of the Scarff – Richardson Bloom score

Appendix The Modified RB score is a composite sum of the factors given below yielding a score from 3 to 9

- Nuclear score (scored from 1, 2, or 3)
- Tubule formation (scored from 1, 2, or 3)
- Mitotic index (scored from 1, 2, or 3)

Mitotic count should be standardized with every microscope and the pathologist should use the same microscope to maintain uniformity

4. Presence and grade of in situ carcinoma (DCIS)

Appendix Grading of DCIS 2,3 –

Grade 1—tumors with non-high nuclear score DCIS without comedo-type necrosis

Grade 2--non-high nuclear score DCIS with comedo-type necrosis

Grade 3—High nuclear score DCIS with or without comedo-type necrosis.

Diagnosis of palpable pure intraduct or in situ carcinoma requires use of markers for myoepithelial cells especially if > 5cm in size, as it may be necessary to distinguish between an invasive tumour with a DCIS like growth pattern, and a true pure DCIS.

5. Extensive intraduct carcinoma /EIC- present/absent 4

Appendix: EIC is defined as the presence of DCIS comprising more than 25% of the total tumour area, encompassed within and immediately outside the invasive tumor confines. It is essential that pathologists take sections of the tumor with a rim of adjacent breast for this purpose.

To evaluate the total DCIS content, draw a hypothetical circle around the most peripheral edges of the tumor. The DCIS that falls within the circle but outside the tumour, plus the DCIS within the main tumour mass, is the total DCIS content. If the sum of the 2 areas is greater than 25% of the whole, it is EIC +ve.

EIC +ve signifies a higher propensity for recurrence, particularly if the margins are positive. Tumors with EIC positive and involved margins require re-excision.

6. Margins – Focal or gross positive for tumor

Appendix

Margin assessment is compulsory for all lumpectomies and wide excisions from breast cancer. It is crucial that the specimen is sent appropriately oriented and labeled for margin evaluation.

Method of margin sampling –

The specimen should be inked before cutting. This is performed by dipping the entire specimen in alcohol briefly, then patting it dry, and finally painting the exterior with an appropriate pigment such as India ink/ any waterproof ink/ Alcian blue.

Lumps < 3cm should be serially sliced either from medial to lateral surfaces or from superior to inferior surfaces, and entirely submitted for histology

For lumps > 3 cm - six shave surface margins from the anterior, posterior, superior, inferior, medial and lateral planes should be given. If tumor is close to a resection margin, then a radial margin should be given.

Reporting a positive margin^{4,5}

Focal positive cut margin is when a margin shows invasive tumor or DCIS in < 3 lpf

Gross positive cut margin is reported when it shows > 3 lpf of invasive tumor or DCIS

Patients with focal positive margins have a 9% risk of recurrence as opposed to 28% with gross positive margins.

7. Lymph node dissection

- Record the total number of nodes dissected.
- Then document the number of involved nodes.
- Document micrometastasis.
- Extension of tumour in perinodal fat
- Presence of emboli in perinodal lymphatics

Appendix 6

Guide lines for node assessment - Nodes should be dissected prior to fixation in formalin. Every node must be submitted for histologic evaluation. One section per node is adequate.

8. Blood vessel and lymphatic embolisation (LVI)

- Evaluate the LVI around the periphery of the tumour and not within it
- The embolus should be near a vein or artery
- The specimen should be well fixed, as cracking and shrinkage artifacts can mimic LVI

9. Hormone Receptor Status by Immunohistochemistry

Appendix- It is essential to fix tissues immediately and appropriately in 10% buffered formalin for IHC demonstration of receptors.

Estrogen Receptor:/ Progesterone Receptor

Interpretation : positivity in > 5% of cells

Scoring- any system may be used – Multiply or add the intensity of staining with percentage of positive cells.

References

- 1) Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*. 1991 Nov;19(5):403-10
- 2) Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. *Lancet*. 1995;345(8958):1154-7.
- 3) Douglas-Jones AG, Gupta SK, Attanoos RL, Morgan JM, Mansel RE. A critical appraisal of six modern classifications of ductal carcinoma in situ

of the breast (DCIS): correlation with grade of associated invasive carcinoma. *Histopathology*. 1996;29(5):397-409

- 4) Schnitt SJ, Abner A, Gelman R, Connolly JL, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. : *Cancer*. 1994;74(6):1746-51.
- 5) Gage I, Schnitt SJ, Nixon AJ, et al Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 1996;78(9):1921-8.
- 6) Fitzgibbons PL , Page DL, Weaver D, et al. Prognostic Factors in Breast Cancer College of American Pathologists Consensus Statement 1999 . *Arch Pathol Lab Med*. 2000;124:966–978.
- 7) Soomro S, Shousha S, Sinnwtt H D. Estrogen & Progesterone receptors in screen detected breast carcinoma: an immunohistological study using paraffin sections. *Histopathology* 1992, 21, 543-547.

Evidence Based Guidelines

Patients are clinically grouped into one of the following categories:

- Operable Breast Cancer
- Large Operable Breast Cancer
- Locally Advanced Breast Cancer
- Metastatic Breast Cancer

Criteria

Operable Breast Cancer:

T < 5cm (T1, T2), N0 or N1 (mobile axillary nodes), M0

Large Operable Breast Cancer:

T > 5cm with no skin involvement (T3), N0 or N1, M0

Locally Advanced Breast Cancer (T4, N2/3, M0)

I. Skin involvement in the form of oedema, ulceration, satellite nodules, infiltration (does not include skin dimpling)

II. Matted or fixed axillary lymph nodes

III. Ipsilateral supraclavicular/internal mammary lymph node(s)

IV. Fixity to chest wall

V. Arm oedema

No evidence of distant metastasis.

OPERABLE BREAST CANCER

Clinical Examination & Investigations:

I. TRIPLE TEST –

1. Clinical Examination of both breasts and axillae
2. FNAC / CORE BIOPSY
3. MAMMOGRAPHY

Note: A strong clinical suspicion for malignancy over-rides both, a negative FNAC or a non-contributory mammography and mandates an excision biopsy.

II. Routine pre-anaesthetic tests including chest X-ray & LFT

III. Incision / Core Biopsy for ER / PgR status if neoadjuvant chemotherapy is planned

Metastatic work up: Is not recommended routinely in operable breast cancer, as the incidence of metastasis is <2% (Updated NCCN guidelines). These tests have a low sensitivity and are not cost-effective.

Surgical Options:

I. Breast Conservative Therapy (BCT) ¹⁻⁵. Wide excision with complete axillary clearance up to apex.

II. Modified Radical Mastectomy (MRM)

NB: Sentinel node biopsy and Axillary sampling, as predictors of the rest of the axilla, are presently investigational procedures and not recommended for use outside research protocols.

Contraindications to BCT:

1. Multicentric disease (> 1 quadrant)
2. Extensive microcalcification on mammogram
3. Doubtful compliance with adjuvant radiotherapy
4. Pregnancy (1[st] / 2[nd] trimesters & precious child)
5. Satisfactory cosmesis unlikely after breast wide excision (relative contraindication)

Options for BCT for relatively large tumours:

- Down-staging with neo-adjuvant Chemotherapy.
- BCT with latissimus dorsi reconstruction

Model Histopathology Report

- Tumour size (all 3 dimensions)
- Tumour type
- Tumour grade (Modified Richardson Bloom Score)
- Presence of extensive intraductal carcinoma (EIC)*
- Lymphovascular embolisation
- Cut Margin status⁶ (gross positive/ focal positive/ negative) in case of lumpectomy or wide excision**
- No. of positive/total axillary lymph node dissected
- Receptor status: ER and PgR (by IHC or EIA)

Note:

* **EIC** is defined as presence of DCIS in more than 25% of any low power field within or outside the tumour and is a strong predictor of local recurrence after BCT.

** **Gross +ve cut margin** is extensive involvement of a cut margin or more than 3 foci of invasive or in-situ carcinoma in any inked margin (Requires revision excision or mastectomy).

** **Focal positive cut margin** is 3 or less foci of invasive or in-situ carcinoma in any inked margin (Revision surgery only if EIC positive).

- **ADJUVANT THERAPY**

Modalities

Systemic: Hormone-therapy⁷⁻¹¹ and or Polychemotherapy¹³⁻¹⁷ and/or monoclonal antibodies

Loco-regional: Radiotherapy^{3-5,17-20}.

Candidates for Adjuvant Systemic Therapy: All women with node-positive breast cancer and / or >1 cm tumor^{16,17}

	ER or PgR +ve	ER & PgR -ve
Premenopausal	Chemotherapy + Hormonal therapy	Chemotherapy
Postmenopausal	Hormonal therapy +/- Chemotherapy	Chemotherapy

Doses and schedules of adjuvant systemic therapy

I. Adjuvant Hormone therapy – To be started after completion of chemotherapy

In Premenopausal patients –

Tamoxifen: 20 mg/day for a period of 5 years⁷

Ovarian ablation considered in pre-menopausal women > 40 years with ER positive tumour.⁸

Ovarian suppression using GnRH analogues like goserelin and leuprolide acetate should be considered in premenopausal patients with T1/T2 N0 ER and/or PgR positive tumours who wish to maintain fertility. Available evidence recommends GnRH analogue therapy for two years.

In Postmenopausal patients –

First five years (disease-free) after surgery –

Tamoxifen: 20 mg/day for a period of 5 years⁷

Tamoxifen: 20 mg/day for a period of 2-3 years followed by **Exemestane** 25mg OD for the remaining 2-3 years⁹

Anastrozole: 1 mg / day for a period of 3 years at least¹⁰

From 5-7 years (disease-free) after surgery –

Letrozole 2.5mg OD for 2 years¹¹

(Patients receiving aromatase inhibitors are at a significantly increased risk for fractures due to osteoporosis. Hence all patients receiving any of the aromatase inhibitors receive prophylactic oral **Alendronate** 70mg once a week)¹²

II. Adjuvant Polychemotherapy (iv bolus or infusion)¹³⁻¹⁹

CAF: D1 only at 3 weekly intervals X 6 cycles

Cyclophosphamide 500 mg/m²

Adriamycin 50 mg/m²

5-fluorouracil 500 mg/m²

CEF: D1 only at 3 weekly intervals X 6 cycles

Cyclophosphamide 500 mg/m²

Epirubicin 90 mg/m²

5-fluorouracil 500 mg/m²

CMF: D1 and D8 at monthly intervals X 6 cycles

Cyclophosphamide 600 mg/m²

Methotrexate 40 mg/m²

5-fluorouracil 600 mg/m²

TAXANES

AC X 4 followed by Paclitaxel X 4: D1 only at 3 weekly intervals X 8 cycles

Cyclophosphamide 600 mg/m²

Adriamycin 60 mg/m²

Paclitaxel 175 mg/m²¹⁶ or 225 mg/m²¹⁷

TAC: D1 only at 3 weekly intervals X 6 cycles

Cyclophosphamide 500 mg/m²

Adriamycin 50 mg/m²

Docetaxel 75 mg/m²

III. Adjuvant Biological Therapy (IV Infusion)

AC X 4 followed by Paclitaxel X 4 with 52 weeks of trastuzumab therapy started concurrently with administration of paclitaxel.

Cyclophosphamide 600 mg/m²

Adriamycin 60 mg/m²

Paclitaxel 175 mg/m² every 3 weeks (NSABP B31 protocol) or 80 mg/m² every week (N9831 protocol)

IV Trastuzumab 4 mg/kg along with first dose of paclitaxel followed by 2 mg/kg weekly for 51 weeks (NSABP B31/ N9831 protocol) or 8 mg along with first dose of paclitaxel followed by 4 mg every 3 weeks (HERA (BIG 0101) protocol)

Three cycles of docetaxel or vinorelbine, followed by (in both groups) three cycles of fluorouracil, epirubicin, and cyclophosphamide with patients with amplified Her-2/neu receiving concomitant trastuzumab infusions (simultaneously with docetaxel or vinorelbine therapy) for a period of 9 weeks. (FinHer Trial)

Word of Caution – *Although one year of adjuvant trastuzumab showed excellent improvements in local and distant disease free survival, the same extent of benefit as not seen in the overall survival probably owing to the increased cardiac failures seen in patients receiving trastuzumab.*

Candidates for Adjuvant Loco-regional Radiotherapy

I. Breast conservation surgery: All patients should receive radiotherapy^{1,3,4}.

II. Post MRM: T >5cm, skin/chest wall involvement or axillary node metastases^{20,21}. In the absence of other risk factors, locoregional RT may be avoided for <4 metastatic axillary nodes if the axillary surgery was adequate¹⁹

III. For women who receive post op RT, the radiation target volume includes Breast / chest wall in all cases and SCF nodes when >3 axillary nodes are +ve¹⁹. Dose recommended: equivalent to 45 to 50Gy / 25# / 5 wks. Tumour bed boost with electrons or 192 Iridium implant (LDR or HDR), equivalent to 10-15Gy is recommended for all BCTs⁵.

Routine postop irradiation of axilla is not recommended unless there is known or suspected residual axillary disease. Similarly, routine irradiation of internal mammary nodes is not recommended pending the results of the large EORTC trial examining the survival benefit of internal mammary RT possible cardiac morbidity / mortality with IMC irradiation^{3,22}.

LOCALLY ADVANCED BREAST CANCER (T4,N2/3,M0)/ LARGE OPERABLE (>5cm) BREAST CANCER (T3,N0/1,M0)

Investigations

- I. Incision Biopsy for tissue diagnosis and receptor study.
- II. Mammography or breast sonography for baseline documentation of tumour size
- III Following Metastatic work-up is recommended

- Chest radiography
- Ultrasound abdomen
- Liver Function Test
- Radionuclide Bone Scan
- Relevant skeletal X-Rays
- Optional – CT Scan and MRI where indicated

Treatment Plan Multi-modal therapy²³⁻²⁶

Sequence Neo-adjuvant chemotherapy followed by surgery followed by completion chemotherapy and then locoregional RT (plus tamoxifen if ER +ve).

- Dose schedules are same as for adjuvant chemotherapy (CAF, CEF)
- Clinical documentation of response at each cycle (primary tumour & nodal size) till maximum tumour shrinkage is achieved (i.e. measurements at two consecutive CT cycles is constant) or there is clinical progression (usually 2 - 6 cycles).
- For patients who are poor or non-responders to anthracyclines, 4 cycles of single agent Docetaxel (100mg/m²) are recommended with up to 55% response rates²⁶

Surgical Treatment Options

- I. If clinical and radiological (mammography) complete response, index quadrantectomy with axillary clearance (BCT).
- II. If partial response with radiological evidence of residual disease, (a) BCT² where feasible or (b) Simple Mastectomy Axillary Clearance (SMAC – The magnitude of the surgery remains the same as in a MRM)
- III. If static disease or progressive disease, SMAC with or without reconstruction for skin cover so that post-operative radiation can be instituted early.
- IV. In case of disease progression locally with inoperability of disease, may consider for preoperative radiotherapy followed by reassessment for surgical excision later.

Completion of remaining cycles of Chemotherapy: (Total 6 cycles) However, if there was no response or disease progression during pre-operative chemotherapy, post operative RT is given first followed by consideration of 2nd line chemotherapy.

Adjuvant Hormonal Therapy – similar to Operable Breast Cancer

Postoperative Radiotherapy: All patients with LABC should receive RT to the breast or chest wall to a dose equivalent of 50Gy / 25# / 5 wks (or 45Gy / 20# / 4 wks). If BCT has been performed a tumor bed boost of 15 Gy in 6 fractions with appropriate electrons is recommended. Routine postoperative irradiation of axilla is not recommended unless there is known or suspected residual axillary disease. Similarly, routine irradiation of internal mammary nodes is not recommended pending the results of the large EORTC trial examining the survival benefit of internal mammary RT possible cardiac morbidity / mortality with IMC irradiation^{3,22} is awaited.

FOLLOW-UP AFTER PRIMARY TREATMENT OF BREAST CANCER

I. Bi-annual **Physical Examination (PE)** for 5 years followed by yearly checkup.

II. **Mammography** once in 18 months.

III. **No other investigations** in asymptomatic patients for early detection of metastasis, since it is -

- Not cost-effective
- Does not prolong survival^{27,28}
- Detection and disclosure of spread of disease may be psychologically harmful to an asymptomatic patient with an incurable metastatic disease.

If recurrence or symptoms suggestive of metastasis, relevant investigations to be done

- Chest radiography
- Ultrasound abdomen
- Liver Function Test
- Radionuclide Bone Scan
- Skeletal survey of suspicious or weight bearing areas
- CT / MRI, where indicated

- **Treatment of Isolated loco-regional recurrence**^{29,30}
- **Resectable: Surgery + radiotherapy**
On completion of loco-regional treatment if there is no evaluable disease then,
tamoxifen (for ER or PgR +ve tumour) till progression²⁹. There is no evidence that early institution of chemotherapy (in ER -ve tumours) prolongs survival, hence it is not recommended.
- **Unresectable or within the field of previous radiotherapy:**
Chemotherapy followed by assessment for surgery.

METASTATIC BREAST CANCER

Goal of management is palliation.

Options & Principles of Management

- Hormone therapy
- Chemotherapy
- Radiotherapy
- Surgery : Pleurodesis, Palliative mastectomy, Spinal decompression, Surgical treatment of fractures when indicated
- Analgesics, Anti-emetics, Sedatives, Anti-depressants, Appetite stimulants as per patient requirements
- Bisphosphonates^{30,31}. For lytic bone metastasis in weight bearing areas: Pamidronate I.V 90mg, 4 weekly or Zoledronic acid I.V. 4mg, 4 weekly as an adjuvant to RT for prevention of fractures & pain relief.
- Others : Nerve blocks

Decision to use chemotherapy or hormone therapy is based on receptor status, disease-free interval (DFI), tempo of recurrent disease and the site of metastasis (whether life-threatening).

Hormone therapy: For ER or PgR +ve ; exclusive bone & soft tissue metastasis, Slow tempo of disease or DFI>1 year.

1st line: Tamoxifen (20 mg) / Letrozole (2.5mg)³²

2nd/3rdline: Letrozole (2.5mg) / Exemestane (25mg) / Anastrozole (1mg)

Medroxy-progesterone acetate: 100 mg tid

Megesterol acetate: 40 mg qid

Oophorectomy - in premenopausal ER & or PgR positive women as second line treatment.

Chemotherapy: For ER & PR -ve disease, Visceral metastasis, Fast tempo of disease or DFI<1 year.

Anthracycline Naïve	CAF / CEF / AC / Trastuzumab ³³ + AC (in her-2 <i>neu</i> positive)
Taxane Naïve	Paclitaxel (3 wkly 135mg infusion over 3hrs) / Docetaxel (3 wkly 100mg infusion over 3hrs) / (Taxanes + carboplatin / adriamycin / capecitabine) ³⁴ / Trastuzumab ³³ + Paclitaxel (in her-2 <i>neu</i> positive)
Post-Taxanes	Gemcitabine ³⁵ / Capecitabine ³⁴ / Mitomycin + Mitoxantrone + Methotrexate / 5-FU / CMF

Radiotherapy:

Bone metastases³⁶: For pain relief, preventing or treating neurological and skeletal complications of bone metastases.

- For isolated or few bone metastases: Localized RT to a dose of 8Gy single fraction or 20Gy/5#/1wk if there is a risk of pathological fracture or impending / established cord compression.
- For widespread bone metastases: Hemi Body Irradiation (HBI); Upper HBI 6Gy / 1#; Lower HBI 8Gy/1#. When both halves of the body have to be treated there should be a interval of 6 weeks.

Brain metastasis: For relieving / preventing neurological manifestation of brain metastases.

- For solitary brain metastases (extracranial disease controlled) AND good performance status: Whole brain RT (30Gy/10#/2wks). Whenever feasible, consider surgical excision prior to whole brain RT or Radiosurgery boost after whole brain RT
- For multiple brain mets OR uncontrolled extracranial disease OR poor performance status: Whole brain RT (20Gy/5#/1wk or 12Gy/2#/3 days).

Choroidal Metastases: Palliative RT (20Gy/5# or 30Gy/10#)

BREAST CANCER SCREENING

- Periodic screening by mammography results in reduction of mortality from breast cancer of about 30%, in women above the age of 50.³⁷
- No convincing evidence of benefit in women <50 years.³⁷
- Mammography breast screening programme is however not sustainable in developing countries.
- Physical Examination (PE) of breast by trained personnel has a sensitivity of 75% and specificity of over 90%³⁸ in detection of breast cancers and may prove to be an alternative to mammography.
- Periodic PE of breast by trained health workers along with health education is being compared with only health education in an ongoing NIH sponsored randomized trial in Mumbai.
- Breast Self Examination (BSE) by patient may help in identifying interval cancers early but there is no evidence that BSE improves survival³⁹.

FAMILY HISTORY OF BREAST CANCER

Family history of breast cancer confers a 2-3 fold increased risk of breast cancer. 5-10% of women have Familial / hereditary breast cancer (3 or more first-degree relatives in successive generations with breast cancer) where the risk is over 50 fold. Hereditary breast cancers are related to mutations in BRCA1 and BRCA2 genes^{40,41}. Genetic testing provides information in a research setting but its use in routine practice needs much evaluation, social debate & counseling. First-degree blood relatives can be tested after confirming mutation in these genes in the index cases. A negative genetic testing does not entirely eliminate the risk of breast cancer, and a positive test cannot be remedied easily or prevented from being transmitted vertically. Such patients should be referred to the cancer genetics clinic for genetic counseling and testing as appropriate.

Treatment options for hereditary breast and ovarian cancer are not well supported by robust evidence. These cancers affect patients younger than 35 years of age and procedures like bilateral mastectomy and oophorectomy, although protective, may have an adverse impact on the Quality of Life of these patients.

BIBLIOGRAPHY

1. Morris AD, Morris RD, Wilson JF, et al Breast conserving therapy versus mastectomy in early stage breast cancer: a meta-analysis of 10-year survival. *Cancer J Sci Am* 1997; 3: 6-12.
2. Chen AM, Meric-Bernstam F, Hunt KK et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. *J Clin Oncol.* 2004 Jun 15;22(12):2303-12.
3. EBCTCG. Effects of radiotherapy and surgery in early breast cancer: An overview of randomized trials. *N Eng J Med* 1995, 333: 1444-1455.
4. Fisher B, Anderson S, Bryant J et al. NSABP. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233-41
5. Bartelink H, Horiot JC, Poortmans P et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *NEJM* 2001; 345:1378-87.
6. Gage I, Schnitt SJ, Nixon AJ et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 1996;78:1921-8
7. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer. *Cochrane Database Syst Rev* 2001;(1):CD000486
8. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation for early breast cancer. *Cochrane Database Syst Rev* 2000;(3):CD000485
9. Coombes RC, Hall E, Gibson LJ et al. Intergroup Exemestane Study A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med.* 2004 Mar 11;350(11):1081-92
10. The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*; 2002 22;2131-9

- 11 Goss PE, Ingle JN, Martino S et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003 Nov 6;349(19):1793-802.
12. Schnitzer T, Bone HG, Crepaldi G et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)*. 2000 Feb;12(1):1-12.
13. Early Breast Cancer Trialists' Collaborative Group. Multi-agent chemotherapy for early breast cancer. *Cochrane Database Syst Rev* 2002;(1):CD000487
14. Piccart MJ, Di Leo A, Beauduin M et al. Phase III Trial comparing two doses of Epirubicin combined with cyclophosphamide with Cyclophosphamide, Methotrexate, and Fluorouracil in node-positive breast cancer. *J Clin Oncol*, 2001 19(12),: 3103-3110.
15. Nabholz JM, Pienkowski T, Mackey J et al. Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study.
16. Henderson IC, Berry DA, Demetri GD et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003 Mar 15;21(6):976-83.
17. Mamounas EP, Bryant J, Lembersky BC et al. Paclitaxel (T) following doxorubicin / cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28 Proc Am Soc Clin Oncol 2003; 22:abstract 12
18. ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer. *Annals of Oncology* 2001. 12: 1047-48.
19. National Institute of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer. Nov 1-3 2000. *J Natl Cancer Inst Monogr* 2001: 30: 5-15.
20. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal breast cancer patients given adjuvant chemotherapy: Danish Breast Cancer Cooperative Group

randomized trial DBCG 82B N Engl J Med 1997; 337:949-55

21. Overgaard M, Jensen MB, Overgaard J et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group randomized trial DBCG 82C. Lancet 1999;353:1641-8

22. Early Breast Cancer Trialists' Collaborative Group. Radiotherapy for early breast cancer. Cochrane Database Syst Rev 2002;(2):CD003647

23. Fisher B, Bryant J, Wolmark N et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. NSABP J Clin Oncol, 16:1998:2672-85

24. Cunningham JD, Weiss SE, Ahmed S et al. The efficacy of neoadjuvant chemotherapy compared to postoperative therapy in the treatment of locally advanced breast cancer. Cancer Invest 1998;16:80-6.

25. Gajdos C, Tartter PI, Estabrook A et al. Relationship of clinical and pathologic response to neoadjuvant chemotherapy and outcome of locally advanced breast cancer. J Surg Oncol 2002; 80: 4-11.

26 Smith I, Heys S, Hutcheon A et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 2002 Mar 15;20(6):1456-66.

27. Palli D, Russo A, Saieva C et al. Intensive vs clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. National Research Council Project on Breast Cancer Follow-up. JAMA. 1999 May 5;281(17):1586.

28. The GIVIO Investigators. Impact of follow-up testing on survival & health-related quality of life in breast cancer patients. A multi-center randomised controlled trial. JAMA 1994; 271: 1587-92

29. Borner M, Bacchi M, Goldhirsch A et al. First isolated loco-regional recurrence following mastectomy for breast cancer: Results of a Phase III multi-center study comparing systemic treatment with observation after excision and radiation. J Clin Oncol 1994;12: 2071-77.

30. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev.* 2002;(2):CD002068.
31. Pavlakis N, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev.* 2002(1):CD003474.
32. Mouridsen H, Gershanovich M, Sun Y et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer group. *J Clin Oncol.* 2001;19:2596-606
33. Eiermann W. International Herceptin Study Group. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. *Ann Oncol.* 2001;12 Suppl 1:S57-62.
34. O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002 Jun 15;20(12):2812-23.
35. K. S. Albain, S. Nag, G. Calderillo-Ruiz et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition).* Vol 22, No 14S (July 15 Supplement), 2004: 510.
36. McQuay HJ, Collins SL, Carroll D et al. Radiotherapy for the palliation of painful bone metastasis. *Cochrane Database Syst Rev* 2000;(2):CD001793
37. Kerlikowske K, Grady D, Rubin SM et al. Efficacy of screening mammography. A meta-analysis. *JAMA* 1995 Jan 11; 273(2):149-54
38. Mitra I. Breast Screening: the case for physical examination without mammography. *Lancet*; 1994; 343:342-344.
39. Thomas DB, Gao DL, Ray RM et al. Randomized trial of breast self-examination in Shanghai: Final results. *J Natl Cancer Inst*; 2002; 94:1445-57.

40. Ford D, Easton DF, Bishop DT et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994; 343:692-5

41. Struwing JP, Hartge P, Wacholder S et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997; 336:1401-8