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 axilla
2. FNAC / CORE BIOPSY
3. MAMMOGRAPHY

Note: A strong clinical suspicion for malignancy over-rules 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 status[6] (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 margi**n is 3 or less foci of invasive or in-situ carcinoma in any inked margin (Revision surgery only if EIC positive).

Staging of the axilla in breast cancer is the single most important prognostic factor which also plays an important role in selection of appropriate adjuvant therapy. Axillary lymph node dissection is however associated with complications of minor lymphodema, pain and parasthesia and seroma formation.

As an alternative technique, sentinel lymph node biopsy has been evolved to stage the axilla. The **Sentinel lymph node** is defined as the first node in the lymphatic basin that receives the primary lymphatic flow from the tumor. The status of the sentinel lymph node is thus proposed to reflect the entire lymph node basin.

The American Association of Surgeon's Guidelines for SNB[42]

The false-negative rate for an individual surgeon as defined during a

- 30-case training set
- must be below 10% for the surgeon to begin performing the procedure as a stand-alone procedure,
- With an identification rate of 85%.

A randomized controlled trial of SNB vs. ALND by Veronesi et al presented in 2003 had a FN of 4.6%. [43] The SNLN was sectioned into 60 sections per node and stained with hematoxylin and eosin. If the result was ambiguous, additional stains for cytokeratins by means of a rapid method (EPOS Cytokeratin reagent with HRP, Dako) and stained for the monoclonal antibody MNF116. While the lymph nodes removed during conventional axillary dissection were

examined by standard techniques. Three to six sections were obtained from each lymph node.

The above mentioned trial had some shortcomings namely:

- Small sample size , N=516
- As per standard guidelines the SLN is sectioned into 2 sections and stained by H&E, if negative cytokeratin stains are used. Veronesi et al sectioned the SLN into 60 sections, 50microm each
- Veronessi et al had a LRREC of >18% with no impact on overall survival however the EBCTCG showed that a difference in LRREC of >10% had an impact on overall survival. This could be explained by the small sample size in the former.

ADJUVANT THERAPY

Modalities

Systemic: Hormone-therapy[7-11] and or Polychemotherapy[13-17] 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]

St Gallens Guidelines:[45]

Risk category	
Low risk T1N0	**Node negative and all** of the following features
	pT,2 cm
	Grade 1
	Absence of PNE
	Her2neu negative
	Age>35
	Endocrine responsive
Intermediate risk Other T1N0 T2N0 Low risk T1-2N1	**Node negative and atleast** one of the following features
	pT>2
	Grade 2-3
	Presence of PNE
	Her2neu Positive
	Age< 35
	Node positive (1-3) and her2neu negative
High Risk High risk T1-2 N1 T1-2 N2-3	**Node positive (1-3) and her2neu amplified** **Node positive (4 or more positive nodes)**

In brief

	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 years[7]

Ovarian ablation considered in pre-menopausal women > 40 years with ER and /or PR 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 years [7]

Tamoxifen: 20 mg/day for a period of 2-3 years followed by **Exemestane** 25mg OD for the remaining 2-3 years[9]

Anastrozole: 1 mg / day for a period of 5 years at least[10]

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

Letrozole 2.5mg OD for 2 years[11]

(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]

Studies which compared Tamoxifen to AI showed an improvement in DFS[10-11] with the use of AI. The Intergroup Exemestane study[9] was first to show an overall survival advantage for switching to Exemestane after 2-3 years of Tamoxifen in hormone receptor positive breast cancer ($p \leq 0.05$). In total, 222 deaths occurred in the Exemestane group compared with 261 deaths in the Tamoxifen group, with a hazard ratio of 0.8 (95% confidence interval: 0.71–1.02; $p = 0.08$). The IES had only

a cause specific mortality benefit with the use of Exemestane. The current evidence for AI is thus only for disease free survival.

II. Adjuvant Polychemotherapy (IV bolus or infusion) [13-19]

A) Node negative:

The EBCTCG overview analysis showed that Anthracycline- containing regimens were associated with a modest but significant reduction in disease recurrence (40.5% vs. 43.2%) and death (28.8% vs. 30.5%) compared to CMF as adjuvant therapy. Further follow-up indicated that the benefit favoring anthracyclines was still evident at 10 years.[44]

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

B) Node positive / High Risk breast cancer patients[45]

The CALGB 9344 trial showed a significant 5-year survival benefit of 80% vs. 77% in women with lymph node-positive disease who received paclitaxel (175 mg/m^2 over 3 hours every 3 weeks × 4) following four cycles of AC, compared to AC alone.[46] This significant trial led to the incorporation and recommendation of paclitaxel following AC administration for adjuvant polychemotherapy in women with lymph node-positive disease.

A metanalysis[47] evaluated the use of Taxanes in early breast cancer Significant differences in favour of Taxanes were seen in DFS (RR: 0.84; 95% CI, 0.79-0.89 [*P*_.0001 and OS in lymph node-positive population (RR: 0.84; 95% CI, 0.77-0.92 [*P*_.0001]). The absolute benefits in DFS and OS in favour of Taxanes ranged from 3.3% to 4.6% and from 2.0% to 2.8%, respectively. The Cochrane metaanalysis pooled the analysis of the trial results which indicated that Texan-containing regimens improved overall survival, with a relative risk reduction of 19% compared to non-Taxane-containing control groups (p<0.00001).2 The absolute risk reduction for Taxane-containing regimens was ~2.6% compared to non-Taxane containing regimens.[48]

No studies have reported results on the use of Taxane-containing regimens in women with node negative disease only

Taxane based regimes:

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/m2[16] or 225 mg/m2[17]

TAC: D1 only at 3 weekly intervals X 6 cycles
Cyclophosphamide 500 mg/m2
Adriamycin 50 mg/m2
Docetaxel 75 mg/m2

TACT: 3 weekly (4CAF- 4T) X 8 cycles

Cyclophosphamide 600mg/m2
Adriamycin 60mg/m2
5-Flurouracil 600mg/m2
Docetaxel 100mg/m2

The trial compared **8 cycles** of FEC_D vs. FEC (60) / E-CMF and the results did not show any overall significant gain from the addition of Docetaxel every 3 weeks to standard Anthracycline chemotherapy of similar duration. There was no significant difference in the DFS between the FEC-D group and the control group (overall HR 0·95, 95% CI 0·85–1·08;). Also there was no observed difference in the 5-year disease-free survival rates. Adjustment for factors known to affect prognosis (ER status, nodal status, HER2 status, age, tumour grade, and tumour size)

gave an HR of 0·93 (0·82–1·05; p=0·25) the anthracycline-docetaxel sequential schedule was associated with a higher frequency of adverse events and transiently poorer quality of life than the non-taxane control regimen.[49]

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 protocol)

For high risk HER-2 positive breast cancer, trastuzumab given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at 3 years by 52%. The addition of trastuzumab reduced the probability of distant recurrence by 53% at 3 years, and the hazard of developing distant metastases appears, thus far, to decrease over time. Results at a median follow-up of 2 years show a statistically significant survival advantage with a relative risk reduction of 33%. [50]

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)

The combination of trastuzumab and chemotherapy has a notable risk of cardiac toxicity. Careful monitoring of cardiac function is of vital importance if trastuzumab is to be used in the adjuvant setting.

NSABP B-31: Post-AC LVEF and age are independent predictors of Trastuzumab-associated CHF

		AGE	
		<50	>50
LVEF	50-54	3/48(6.3%)	9/47(19.1%)
	55-64	5/229 (2.2%)	10/194(5.2%)
	65+	1/160(0.6%)	2/159 (1.3%)

Candidates for Adjuvant Loco-regional Radiotherapy

I. Breast conservation surgery: All patients should receive radiotherapy[1, 3, and 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 adequate[19]

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 +ve[19]. 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 BCTs[5].

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/ Taxanes)
- 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/m^2) are recommended with up to 55% response rates[26]

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) BCT[2] 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 progression[29]. 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 Zolendronic 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 *neu* positive)
Taxane Naïve	Paclitaxel (3 wkly 135mg infusion over 3hrs) / Docetaxel (3 wkly 100mg infusion over 3hrs) / (Taxanes + carboplatin / adriamycin / capecitabine)[34] Trastuzumab[33] + Pacltaxel (in her-2 *neu* positive)
Post-Taxanes	Gemcitabine[35] / Capecitabine[34] / Mitomycin +

	Mitoxantrone + Methotrexate / 5-FU / CMF

Radiotherapy:

Bone metastases[36]**:** 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 survival[39].

FAMILY HISTORY OF BREAST CANCER

Hereditary breast cancers are related to mutations in BRCA1 and BRCA2 genes[40,41] 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.
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.
The question still to be answered is if an asymptomatic person tests positive for BRCA1/ BRCA2 mutation what is the appropriate line of management in such a case. The current recommendations include the need for increased frequency of mammography, breast self examination, clinical breast examination, screening for ovarian cancer. 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.

In a landmark study Hartmann et al analyzed a retrospective cohort of women with positive family history of breast cancer who underwent a bilateral prophylactic mastectomy. The analysis performed at the Mayo clinic had a >90% reduction in the incidence of breast cancer and reduction in mortality in both the high risk and moderate risk groups.[51] However the effect on QOL is a major factor that necessitates careful use of prophylactic mastectomy in patient with the gene mutation.

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