CONSENSUS DOCUMENT FOR MANAGEMENT OF BREAST CANCER

Prepared as an outcome of ICMR Subcommittee on Breast Cancer

Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
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Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

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CHAPTER 1

BREAST CANCER IN INDIA AND NEED FOR MANAGEMENT GUIDELINES

Breast cancer is the most common female cancer in the world with an estimated 1.67 million new cancer cases diagnosed in 2012. While the age adjusted incidence rates of breast cancer in India is lower than the western countries, because of the large population the burden of breast cancer is high. With an annual incidence of approximately 1,44,000 new cases of breast cancers in India, it has now become the most common female cancer in urban India[1].

There is general consensus in Indian oncologists regarding the use of surgery, with breast conservation when feasible and the indication for radiotherapy, chemotherapy and hormone therapy in various stages of breast cancer. Breast conservation rates are low even for stage I & II breast cancers in most Indian centres and reflects the lack of access to modern radiotherapy. The quality of mastectomy, axillary lymph node dissection and pathology reporting varies significantly across the country. The choice of chemotherapy regimen and hormonal agents for different stages of breast cancer is determined not only by the prognostic and predictive factors but also by the logistics and access. Similarly the treatment for recurrent or metastatic disease is not uniform and is governed by several factors including the previous treatment, patient's ability to tolerate additional treatment and access to such treatment. For Indian women with operable breast cancer who received standard multimodal treatment in the control arm of a recently published large randomized clinical trial from Tata Memorial Hospital (TMH), the 5 year disease free survival (DFS) rate of 70% and overall survival rate of 78% was reported[2].

In resource constrained countries with low per capita income, high out of pocket expenses on health care and long waiting lists in publically funded institutes, threshold for adopting a diagnostic or therapeutic approach in routine practice requires careful consideration of the strength of evidence for long term clinical benefit, resource implications and cost effectiveness. Safe and effective strategies should be developed, standardized and propagated taking in account the feasibility of safely executing them in majority of departments across the country. Despite major advances in terms of availability of modern technology in India and expertise to use it in the last decade, a significant proportion of cancer patients either do not have access to or cannot afford state-of-the-art treatment. Hence there is a need to define the scope and limitations of approaches that would be more accessable or affordable and what would be considered ideal in western countries.

Several international and national consensus guidelines from professional bodies and expert panels are available for the management of breast cancers. The widely used international guidelines are from the National Comprehensive Cancer Network (NCCN)[3], St.Gallen International Expert Consensus[4] and the European Society of Medical Oncology (ESMO)[5-7] and the National Institute for Health and Care Excellence (NICE) of the U.K[8]. These are based on evidence from clinical trials from a patient population which in general has better tolerance to systemic chemotherapy and greater access of high quality care required for optimal management of acute and late complications of treatment. Therefore, it is important

to formulate guidelines which takes in to account not only the robust scientific evidence generated through large randomized trials in the western population but also the feasibility of implementing them in routine clinical practice, differences in patients tolerance and wherever it is available, the Indian data and experience. Few Indian guidelines and expert consensus statements covering major aspects of breast cancer management are also published[9,10].

Considering that there are very few large randomized trials or prospective studies from India and there are notable differences in the age and disease stage at presentation one has to exercise caution in directly extrapolating results of RCTs conducted in the west to our population. Providing treating doctors with uniform guidelines for the management of Breast cancer appears to be an appropriate step forward in achieving this goal.The following chapters review the existing National and International guidelines for breast cancer and their applicability in the Indian context.

CHAPTER

2 BREAST CANCER EPIDEMIOLOGY AND SCREENING

In India the incidence of breast cancer is significantly lower than western countries. Breast cancer in India varies from as low as 5 per 100,000 female population per year in rural areas to 30 per 100,000 female population per year in urban areas[11]. There is an impression of higher incidence of breast cancer in younger women in India as most hospital based series report median age of breast cancer patients a decade younger than western series. However this may be due to a combination of the population structure and inherent bias against referral, treatment and ascertainment of breast cancer in the elderly in India rather than a true reflection. The incidence of breast cancer increases with age and this is true in India like rest of the world. With the exception of 5-10% breast cancers where the main risk factor is genetic predisposition, in the remaining 90% of sporadic breast cancers, the identified risk factors are either reproductive, lifestyle or environmental factors, primarily through their influence on the hormonal milieu. No breast cancer risk factor, unique to the Indian population has been widely reported.

Breast cancer screening using various approaches has been the subject of several large randomized trials in USA, Canada and Europe. Population-based mammographic screening of asymptomatic postmenopausal women has shown a modest reduction in breast cancer deaths in high incidence affluent western countries but with associated over diagnosis and overtreatment[12].

However population-wide mammographic screening program of asymptomatic women is neither feasible in India nor it may be as useful due to lower breast cancer incidence and population structure in India[13]. Opportunistic screening may be considered for some high risk and concerned women in India.

Periodic physical examination 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[14].

Breast Self Examination (BSE) by women may help in identifying breast tumors earlier but there was no reduction in breast cancer mortality in one randomized screening trial of BSE versus no intervention[15].

CHAPTER

3 STAGING AND PROGNOSTIC CRITERIA

Breast cancer staging is done after careful clinical evaluation and appropriate investigations as described in the next chapter. The staging system has evolved over the decades from simple classification of breast cancer as operable, inoperable to metastatic cancer to more detailed UICC and AJCC TNM system. The two commonly used staging system are outlined here.

PRAGMATIC CLINICAL STAGING SYSTEM	
A)	**Operable Breast Cancer (OBC): T1-2, N0-1,M0**
	T1-2: Primary Tumor size up to 5 cm without skin or chest wall involvement
	N0-1: Clinically uninvolved axilla or mobile axillary nodes
	M0: No metastatic disease on relevant investigative work up
B)	**Large Operable Breast Cancer (LOBC): T3, N0-1,M0**
	T3: Primary tumour size >5 cm without skin or chest wall involvement
	N0-1: Clinically uninvolved axilla or mobile axillary nodes
	M0: No metastatic disease on relevant investigative work up
C)	**Locally Advanced Breast Cancer (LABC): T4 or N2-3,M0**
	T4: Primary Tumor of any size but involves skin or chest wall
	N2-3: Matted or fixed axillary nodes or supraclavicular or internal mammary nodes
	M0: No metastatic disease on relevant investigative work up
D)	**Metastatic Breast Cancer (MBC): Any T or N stage with distant metastasis (M1)**

TNM STAGING SYSTEM (Clinical)	
Primary tumour	
Tx	Primary tumour cannot be assessed
Tis	In Situ carcinoma
T1	Primary Tumor size up to 2 cm without skin or chest wall involvement
T2	Primary Tumor size up to >2 cm up to 5 cm without skin or chest wall involvement
T3	Primary tumour size >5 cm without skin or chest wall involvement
T4	Primary tumour involves skin, chest wall, satellite nodules or inflammatory breast cancer
T4a	Involves chest wall
T4b	Involves skin
T4c	Involves skin and chest wall
T4d	Inflammatory breast cancer
Lymph nodes	
Nx	Nodes cannot be assessed
No	Clinically uninvolved axilla
N1	Mobile ipsilateral level I or II axillary nodes

N2a	Matted or fixed ipsilateral axillary nodes
N2b	Ipsilateral Internal Mammary Nodes (IMN) without axillary nodes
N3a	Ipsilateral Infraclavicular lymph nodes
N3b	Ipsilateral IMN + axillary nodes
N3c	Ipsilateral Supraclavicular nodes
Metastasis	
M0	No metastatic disease on relevant investigative work up
M1	Metastatic disease

TNM STAGING SYSTEM (Pathological)	
Primary tumour	
pTx	Primary tumour cannot be assessed
pTis	In Situ carcinoma
pT1	Primary Tumor size up to 2 cm without skin or chest wall involvement
pT2	Primary Tumor size up to >2 cm up to 5 cm without skin or chest wall involvement
pT3	Primary tumour size >5 cm without skin or chest wall involvement
pT4	Primary tumour involves skin, chest wall, satellite nodules or inflammatory breast cancer
pT4a	Involves chest wall
pT4b	Involves skin
pT4c	Involves skin and chest wall
pT4d	Inflammatory breast cancer
pNx	Nodes cannot be assessed
Lymph nodes	
pNo	No regional lymph node metastasis identified histologically
pN1mi	Micro-metastasis (> 0.2 mm but < 2.0 mm)
pN1a	1-3 axillary nodes
pN1b	Ipsilateral Internal Mammary Nodes (IMN) on sentinel node biopsy without axillary nodes
pN1c	N1a + N1b
pN2a	4-9 axillary nodes
pN2b	Clinically apparent IMN without axillary node metastasis
pN3a	10 axillary LNs OR Infraclavicular LNs involved.
pN3b	Clinically apparent IMNs + positive axillary nodes OR >3 axillary nodes + IMN only on SLN biopsy
pN3c	Ipsilateral supraclavicular lymph nodes
Metastasis	
M0	No metastatic disease on relevant investigative work up
M1	Metastatic disease

CHAPTER

4 DIAGNOSTIC EVALUATION AND STAGING WORK UP

Breast cancer is prone to systemic spread, the probability of which increases with tumour size, local infiltration and lymph node metastasis. Some investigations are essential for clinical management, especially if the desirable investigations are not feasible due to various reasons and indicated against each investigation for different stages of the disease.

	OBC	LOBC/LABC	MBC	Purpose/ Comments
RoutineTests (CBC, Biochemistry)	YES	YES	YES	To assess fitness for anesthesia & chemotherapy
Breast Imaging (see flow chart)	YES	YES	*In selected cases where it is clinically indicated	**B/LMammography**: If the breast lump is suspected to be malignant, especially if BCT is being considered. **USG:** If cystic/ benign lesion is suspected, especially in young women **MRI:** In expert centres breast MRI is useful in screening or characterizing breast lump if mammography is sub-optimal due to dense breast (as in some young women) or prior breast reconstruction. Specially useful for screening young women at high risk of developing breast cancer due to family history or BRCA mutation
Cytological/ Histopathological Confirmation of diagnosis	YES	YES	YES	**Core biopsy:** Preferred method in all cases and mandatory if Neo- adjuvant systemic therapy is planned for histological grading and receptor status. To mark the site of the primary tumor the core biopsy should be centered over the tumor. **FNAC:** is acceptable in cases with clinical and mammographically evident cancer planned for upfront surgery. **Incision or Excision Biopsy:** When there is high clinical suspicion and repeated FNAC/core biopsy are negative
ER/ PR	YES	YES	YES	IHC (>1% tumour cells staining for ER considered ER+ve)[16].
HER2	#YES	#YES	#YES	#More relevant in cases for whom Traztuzamab is feasible Standardized IHC for HER2; If IHC is equivocal (2+) then FISH
ChestX Ray	YES	YES	YES	To assess fitness for anesthesia and for staging in LOBC / LABC
[17]BoneScan	*No	^YES	^YES	*If raised Alkaline Phosphatase or bone symptoms/sign ^If Bone scan not feasible due to various logistical or healthcare provision issues, perform Skeletal survey, especially if symptomatic.

[17]USGAbdomen	*No	^YES	^YES	*If abnormal LFT or suspicious symptoms / signs. ^Not required if CT Thorax & Abdomen is being performed
[17]CTThorax /Abdomen	*No	^YES	^YES	*If abnormal LFT or suspicious symptoms / signs. ^If CT Scan is not feasible due to various logistical or healthcare provision issues, Chest X Ray and USG Abdomen for staging
FDG PET/CT Scan	No	#In selected cases	#In selected cases	#Specially useful if standard imaging findings are equivocal.
Tumour markers (CA-15.3 etc)	No	No	No	Clinical Utility in making diagnosis and disease monitoring not yet established
Multi-gene Signature Mammaprint and Oncotype Dx	*No	Notapplicable	Not applicable	Their clinical utility and added value in routine practice is as yet unknown and there is very little data in the Indian patients. Recently an IHC4 test (ER,PR, HER2 and Ki-67) seems to provide useful information and is advocated by NICE in research settings

Partly adapted from NCCN/ ESMO/ NICE practice guidelines)[4-9]

4.1 EVALUATION OF A BREAST LUMP

All women with a breast lump should undergo a TRIPLE TEST comprising of

1. Clinical Examination by experienced clinician, preferably a breast surgeon.

2. Breast Imaging#: Bilateral Mammogram and or Ultrasound or MRI as appropriate.

3. Histopathology*: FNAC / Core biopsy (Ideal). Excision Biopsy/Incision biopsy if indicated.

Based on clinical examination and appropriate breast imaging the lump can be classified as cystic or solid. Based on the index of suspicion for malignancy (age, clinical finding, family history or previous breast biopsy findings) solid lesions can be further characterized as likely benign or suspicious for cancer. This will be the basis of their further evaluation as described below:

A) CYSTIC[18,19]: Breast Ultrasound followed by clinically guided or USG guided cyst aspiration. Women with small multiple cysts or if there is clear fluid on aspiration can be observed. Cytology / histopathology evaluation* is advised for cysts which are complex or hemorrhagic, refill rapidly or have a residual lump.

B) SOLID BENIGN: Should be evaluated with breast imaging# and excision biopsy if solid

C) SUSPICIOUS SOLID: Should be evaluated with breast imaging# and if on imaging the lump is still suspicious it should be evaluated with cytology / histopathology*

BENIGN: Excision biopsy

MALIGNANT: Follow relevant algorithm

IMAGING MODALITY FOR BREAST LESIONS

1. If clinically it is a cyst: evaluate by USG.
2. If less than 30yrs and clinically benign: evaluate by USG.
3. If above 30 yrs or below 30 yrs with clinical suspicion: evaluate by Mammography+/-USG.

4. While there is no defined role of routine breast MRI prior to Breast Conserving surgery[20], in centres with experience in Breast MRI, it may be used in women with

   a. Premenopausal women with dense breasts & equivocal mammogram if BCT is planned.

   b. Screening high risk women due to family history or BRCA mutation[8].

   c. Axillary node metastasis without clinical/mammographic evidence of breast primary.

   d. Optimal mammographic evaluation is not possible due to breast reconstruction or implants.

*HISTOPATHOLOGY CONFIRMATION:

1. Core biopsy is preferred for all cases, especially if Neoadjuvant chemotherapy is planned (for grading and receptor status) and for guided biopsy of non-palpable lesion. Biopsy to be centered over the tumor to mark it location.
2. In our country with infrastructure issues, FNAC is acceptable provided multiple passes are done & quality smears are prepared. On site evaluation with rapid Diff Quick Stain ensures reducing number of non diagnostic FNAC's.
3. For papillary tumors and intraductal carcinoma, excision biopsy for definite diagnosis.
4. Incision/Excision Biopsy: If high clinical suspicion and repeated FNAC or core biopsies are negative.
5. Frozen section is useful in expert centres if all above fail. Not recommended for papillary lesions & complex sclerosing lesions.

4.2 EVALUATION FOR NIPPLE DISCHARGE

Based on detailed history and clinical examination, in women without any associated breast lump or abnormal mammogram, further evaluation is based on the colour of the nipple discharge as described below:

A) Galactorrhoea/White:

If the woman is not lactating or pregnant then serum prolactin and thyroid profile should be done and reassessed

B) Grumous/Greenish:

Consider a course of antibiotics if the nipple discharge is not blood stained and negative for RBC, especially if it is associated with inflammation. Should be reassessed.

C) Serous/Yellow/Blood-stained:

Perform breast imaging with mammography and or USG

1. **Single duct involved:** For spontaneous, profuse, blood stained discharge or presence of RBC on cytology, consider excision of the duct (**Microdochectomy**)
2. **Multiple ducts involved:** For profuse multiple duct involvement especially in postmenopausal women, consider **Hadfield's surgery.**

CHAPTER

5 MANAGEMENT OF BREAST CANCER

Management of breast cancer depends on several patient related factors, disease stage and predictive and prognostic factors as outlined below

1. Age
2. Menopausal status
3. Family history of cancer
4. Comorbidities especially pre-existing cardiac conditions and long standing poorly controlled hypertension, diabetes or obesity
5. Performance status and adequate renal and liver function
6. Tumor size and infiltration of skin or chest wall
7. Involvement of nipple with Paget's disease or nipple discharge
8. Radiological characteristics of the primary tumour – especially the nature and extent of micro-calcification
9. Site and extent of nodal metastasis
10. Distant metastasis if any, its site (bone only or visceral) and extent
11. Histological features like grade, lymphatic invasion, resection margins and EIC
12. Estrogen or Progesterone receptor status of primary or recurrent tumour or metastatic sites
13. HER-2 expression in primary or recurrent tumor or metastatic sites
14. Proliferative markers and gene signature in some cases
15. Psycho-social and body image issues
16. Patients wishes
17. Patients likely compliance with full treatment and follow up
18. Access to health care, family and social support and affordability

5.1 Management Algorithm for DCIS and DCIS with Micro-invasion

Ductal Carcinoma *In Situ* (DCIS) is being increasingly diagnosed in the west due to widespread use of screening mammography. The natural history of screen detected DCIS is variable and many of these will not progress and may have remained clinically silent during the women's lifetime.

Imaging for DCIS is similar to breast cancer and takes in to account the patient's age, breast density and whether breast conservation is planned or not.

Core Biopsy is necessary for histopathological confirmation. For impalpable lesions it should be image guided biopsy and performed in centres with experience.

Surgery followed by tamoxifen is the mainstay of treatment. Post-operative RT is required after BCT in women at higher risk of recurrence as described below.

Lumpectomy[21,22] with Axillary Sampling or Sentinel Node Biopsy[23] is considered for DCIS without diffuse micro-calcification or multicentric disease.

Simple mastectomy[21] with or without reconstruction is performed for large or multicentric DCIS or when there is diffuse micro-calcification.

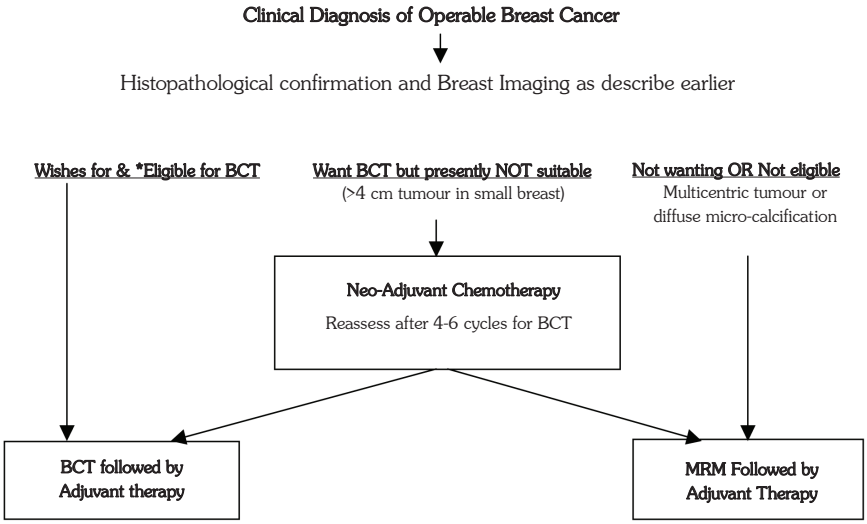
Adjuvant treatment with **Tamoxifen** (for ER/PR +ve tumors) or Radiotherapy after lumpectomy reduces the risk of local recurrence of DCIS and invasive cancer[24-26]. Tamoxifen also reduces risk of contralateral DCIS and cancer.

Use of adjuvant Tamoxifen and Radiotherapy (after lumpectomy) is guided by the University of Southern California / Van Nuys Prognostic index (USC/VNPI). This stratifies a patient into high (10-12), intermediate (7-9) or low risk (4-6) based on the criteria which individually scores as 1, 2 or 3 as described below:

- Age (>60, 40-60, <40)
- Tumor grade & comedo necrosis (low grade, high grade without comedo necrosis, high grade with comedo necrosis)
- Tumor size (≤1.5cm, 1.6-4cm, ≥4.1 cm)
- Margin from resection (≥10mm, 1-9mm, <1mm)

Palpable DCIS with or without micro-invasion is the most common presentation of DCIS in India. In such scenario, role of adjuvant chemotherapy should be carefully considered especially in HER2/neu +ve and ER/PR –ve DCIS or micro-invasive tumors[27].

5.2 Management Schema in Operable Breast Cancer (T1-2, N0-1, M0)



Neo-Adjuvant & Adjuvant Systemic Therapy (Chemotherapy, Hormone Therapy and Biological agents): Individualized as per the disease stage, menopausal status, receptor status, other prognostic or predictive factors along with the tolerance, compliance, feasibility and cost-benefit aspects of a particular approach. Indication, regimes and sequencing are described later in this document.

Adjuvant Radiotherapy: Post Operative radiotherapy (usually after completion of chemotherapy) is indicated in all patients undergoing BCT and after mastectomy if T3 or +ve resection margins or >3nodes. For

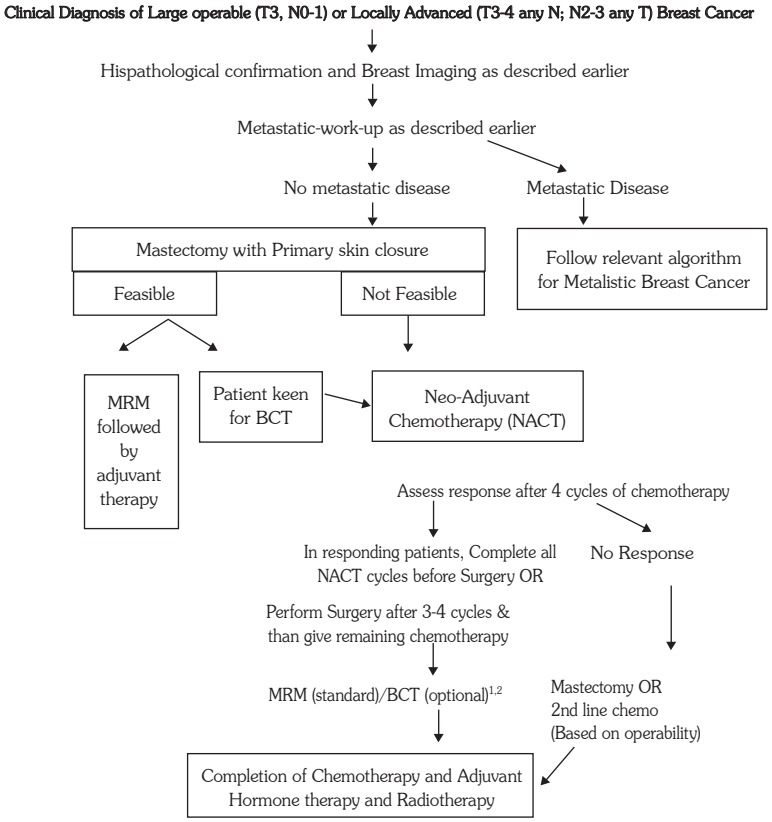
1-3 +ve nodes, it is being increasingly considered as discussed later. Accelerated Partial Breast Irradiation (APBI) with various techniques is an option for highly select cases in experienced centres. RT indications and dose regimes are described later.

***Eligibility for BCT:** The breast conservation approach would be considered successful if it produces satisfactory cosmetic outcome and the probability of tumor control or late sequelae are not inferior to mastectomy. This requires careful evaluation and selection of cases; good quality breast imaging; wide excision of primary with appropriate axillary surgery by experienced surgeons; meticulous histopathological evaluation and reporting of resected specimen; quality assured technique of radiotherapy delivery to standard doses and regular clinical and mammographic follow up to detect and salvage breast recurrences early. This would require infrastructure, equipment (e.g. LINAC which is required in >75% BCT cases) and expertise. Centres with requisite facilities and expertise (sometimes shared between the referring and the referral centre) should offer BCT to eligible women or if they lack such facilities refer the eligible women who wish to conserve their Breasts to such centres.

Absolute contra-Indication: Diffuse micro-calcification; multicentric tumor involving >1 quadrant; resection margins +ve on repeated excisions and EIC+; serious concerns over patient's likely compliance with RT and follow up; rare syndromes of radiation hypersensitivity; previous chest/ breast RT.

Relative contra-indication: If lump to breast size ratio precludes acceptable cosmesis even after NACT, BCT with acceptable cosmetic outcome can be obtained with reconstruction or oncoplasty in expert centres.

5.3 Management Schema in Large Operable or Locally Advanced Breast Cancer



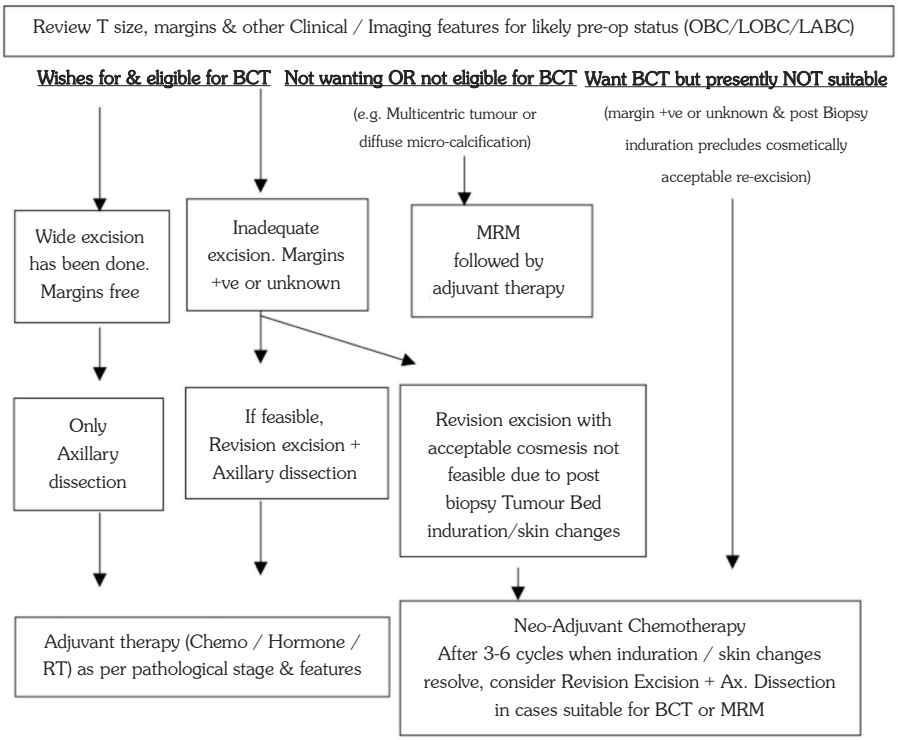
Systemic Therapy: Chemotherapy, Hormone Therapy or Biological agents are individualized as per the disease stage, menopausal status, ER/ PR/Her2, other prognostic or predictive factors along with the tolerance, compliance, feasibility and cost-benefit aspects of a particular approach as described later.

Adjuvant Radiotherapy: Post Operative radiotherapy, usually after completion of chemotherapy to all LOBC /LABC patients irrespective of the type of surgery. Radiotherapy regimes described later.

Ref: *1. Parmar V et al(2006) Int J Surg 4:106–114. 2. Mamounas EP et al.ASCO Breast Symp 2010. Abstract 90*

5.4 Management Schema for patients presenting after lumpectomy / excision elsewhere with or without sufficient clinico-pathological information (a common presentation)

- Detailed history for the site and size of primary and features suggestive of skin involvement.
- Clinical examination for breast scar, indurations, residual lump, skin, nodal and distant sites.
- Review pre biopsy breast imaging films & reports if available and repeat if feasible
- Review pathology report and blocks, if available, for tumor size, margins, type, grade, ER/PR
- Metastatic-work-up if features of LOBC/ LABC cannot be ruled out.



Systemic Therapy: Use of chemotherapy, hormone therapy and biological agents is individualized as per the disease stage, menopausal status, receptor status, other prognostic/ predictive factors & the tolerance /compliance/feasibility/cost-benefit aspects of a particular approach. Indication, regimes and sequencing described later in this document.

Adjuvant Radiotherapy: Post Operative radiotherapy, usually after completion of chemotherapy to all women undergoing BCT and all women undergoing mastectomy if LOBC /LABC cannot be reliably ruled out. Radiotherapy fields and dose regimes are described later.

CHAPTER

6 SURGERY FOR BREAST CANCER

The indications for BCT or mastectomy and its sequencing with chemotherapy are described in the previous chapter on management algorithms. Indications for special surgical procedures are described here.

Sentinel node biopsy and Axillary sampling: Several RCTs [28,29] show that in women with small tumors and clinically negative axilla, the morbidity from axillary dissection done as a therapeutic or staging modality can be avoided by careful histological examination of the sentinel lymph nodes identified by various methods and conducting full axillary dissection only in those with positive sentinel nodes. Sentinel Node Biopsy (SNB) is performed using 0.3ml sub-dermal injection of patent blue dye or 2% methylene blue 10 minutes prior to the surgical incision and 0.5ml of technetium–labeled sulphur colloid 2 hours prior to surgery. The technique should be validated in each centre for its sensitivity and specificity before offering it as a routine. Low axillary sampling, an alternative to SNB can be practiced more widely in developing countries. If histological evaluation of sentinel lymph nodes or low axillary sampling does not reveal any metastasis, completion axillary clearance is not warranted. However, if the SNB is positive or the paraffin sections show metastasis, completion axillary clearances (Level I – III) are generally considered. There is however recent EORTC-AMAROS RCT showing that in SNB + ve cases, axillary RT achieves axillary control rates similar to completion axillary clearance but with different morbidity pattern (Donker et al, Lancet Oncol. 2014).

Breast reconstruction: In centres with such expertise, breast reconstruction should be offered to women who are likely to have a poor cosmetic outcome after BCT or are undergoing mastectomy and not at excessive risk of local recurrence or wound complication. Because of the resource constraints and optional nature of this service, few centres in the country, especially in the busy public hospitals, routinely offer or perform breast reconstructions for majority of the patients who may benefit from such reconstruction. Hence good quality breast reconstruction services may be prioritized.

Whole breast reconstruction (WBR) with or without nipple areolar reconstruction should be offered to motivated young women who have to undergo a mastectomy for a DCIS or early breast cancer (for reasons such as diffuse micro-calcification or multi-centric disease) or as a prophylactic surgery as in BRCA1 mutation carriers. Reconstruction could be immediate or delayed. WBR can be done with **pedicle flap** (Latissimus dorsi flap with implant or expander or a Transverse Rectus Abdominis Myocutaneous flap) or as a **Free flap with microvascular anastomosis** (Deep Inferior Epigastric perforator flap; Anterolateral thigh flap or Superior Gluteal artery perforator flap)

Partial breast reconstruction (PBR): Is indicated after upfront surgery for large tumor with micro-calcification or after NACT with unfavourable breast to tumor ratio and patient is keen on breast conservation. Reconstruction can be done using autogenous tissue (fat, muscle, skin and vasculature) from the back (latissimus dorsi flap), abdomen or thigh as a free or pedicled flap.

CHAPTER 7

HISTOPATHOLOGICAL EVALUATION AND REPORTING

Optimal management of breast cancers hinges upon standardized histopathology evaluation and reporting[30] .

All specimens should be transported to the pathology lab immediately. In case a delay is expected surgeons should slice specimen's posterior aspect upwards.

All lumpectomies should be treated as potentially harboring cancer and should be oriented for margin evaluation. A six surface margin (anterior, posterior, inferior, superior, medial and lateral) is sufficient for routine evaluation though more extensive sampling may result in greater margin positivity. Close margins are to be evaluated radially whereas shave margins should be evaluated for further margins.

All specimens should be fixed in 10% neutral buffered formalin with pH7.2 to 7.4. Sections for ER/PR/Her2neu estimation should be fixed for no less than 6 hours and no more than 72 hours before processing. ASCO-CAP guidelines suggest recording the time specimen is out of patients body and time specimen is fixed in formalin for validating specimen fixation. ASCO-CAP guideline state "It is the responsibility of the surgeon and operating room staff or the radiologist and his/her staff obtaining the specimen to document the collection time, and it is the responsibility of the pathologist and laboratory staff to document the fixation start time".

For lymph nodes, record the number, size of largest node and number of grossly metastatic nodes. One section from grossly metastatic nodes is enough. For lymph nodes>5mm in maximum size slice at approximately 3mm or less perpendicular to the long axis. Lymph nodes <5mm should ideally be bisected and blocked; alternatively, lymph nodes <5mm can be blocked in their entirety. Nodes should be counted even on microscopy to avoid duplication of nodes during submission.

For sentinel node, slice at 2mm interval and submit entirely. If the initial H&E stained section is negative, four levels are cut. Three of these sections are stained by H&E and one randomly chosen section is stained with an epithelial IHCstain.

Sections to be taken

Lumpectomy

A: Four sections from tumor all with adjacent normal breast;

B to G: Six surface margins;

H: Remaining Axillary /apical nodes

Mastectomy

Specimens are evaluated similarly but base is the only relevant margin.

Nipple areola and overlying skin should be evaluated whenever included in specimen.

All mammographically detected lesions should be grossed under mammographic guidance. Make sure to block the entire lesion so as that the size of lesions can be reconstructed microscopically. Also sample margins of lesions radiologically.

Essentials in a Histopathology report:

- Tumor size (all 3 dimensions)
- Tumor type
- Tumor grade (Modified Richardson Bloom Score)
- Presence of extensive intraductal carcinoma (EIC)*
- Lymphovascular emboli
- Margin status (negative /close /focal positive /gross positive) in wide excision**
- No.of metastatic nodes and total axillary lymph node dissected
- Receptor status: ER and PR (by IHC or EIA) and HER2neu by IHC. ER and PR should be scored as described later.**
- HER2neu of 2+ on IHC is considered equivocal and this can be resolved by FISH test for gene amplification, which is considered amplified or positive if score >2.2.

***EIC:** DCIS in >25% of any low power field within or outside the tumor. It is a strong predictor of local recurrence after BCT, especially if margins are positive.

****Gross +ve cut margin:** Extensive involvement of a cut margin OR >3 foci of invasive or in-situ carcinoma in any inked margin. It requires revision excision or mastectomy.

****Focal positive cut margin:** 3 or less foci of invasive or in-situ carcinoma in any inked margin. It requires revision surgery especially if EIC is present

Modified Richardson Bloom grading system (Nottingham's modification)

	Tubule	Nuclear grade	Mitosis/10hpf*
Score1	>75%	Small uniform nuclei, no pleomorphism	0-6
Score2	10-75%	Moderate sized nuclei with pleomorphism	7-12
Score3	<10%	Marked pleomorphism	>12

Final score 3-5=Grade I, Final Score 6-7=Grade II, Final Score 8-9=Grade III

*Could vary with microscope.

- Grade all carcinomas, including post NACT, special types and core biopsies.
- ER/PR estimation should be routinely performed. ERPR expression in >1% of cells is reported as positive for hormone receptors. For ER/PR estimation it is crucial to fix tissues in 10% neutral buffered formalin and employ pressure cooking methods for antigen retrieval. When reporting on outside referral material, if fixation procedure is not documented, poor quality of fixation, if evident, should be commented. Though ASCO-CAP guidelines suggest that such samples should be rejected, it is not feasible in many Indian practice settings. Including normal breast tissue along with tumor section helps to asses internal control for hormone receptor and validate a given test result[31,32].

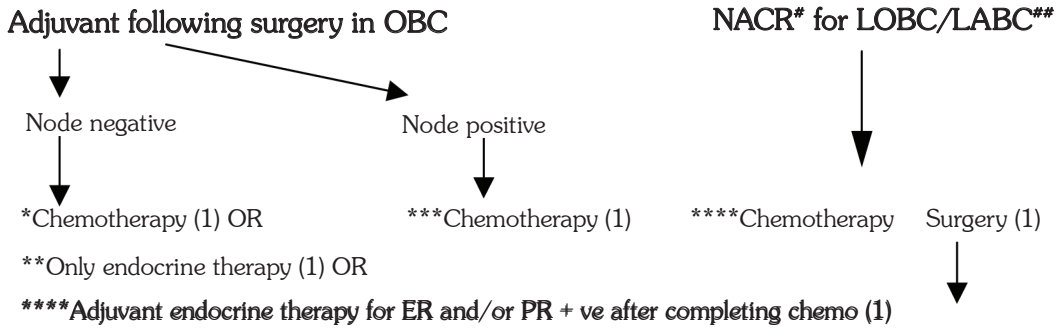
- Her2neu IHC testing should ideally be done by the FDA approved Hercep test OR Ventana Her2neu assay. However these FDA approved assays are not commonly used in India due to their cost. Hence before using any non validated antibody in routine practice, the laboratory should validate it either with FISH or the FDA approved IHC assays. Any Her2neu IHC showing membranous staining of normal breast epithelium should be reevaluated. Since patients with IHC score 3 may receive Trastuzumab without FISH confirmation, strict guidelines for interpretation and reporting should be followed. Only a complete and crisp membrane staining without any cytoplasmic staining in >30% of cells should be interpreted as score 3 or positive. Score 2 staining results in complete membrane staining but in <30% of cells and considered equivocal. All other staining is negative (score1/0). For FISH, count non overlapping cells and select block for invasive tumor. Reject FISH if signals are non-uniform, background obscures interpretation, autofluorescence[33].
- Ki67 correlates with tumour grade and can provide useful additional prognostic information in low grade tumours. Validated Ki67/MIB1 testing in node negative, small, low grade tumours can help decide the need for chemotherapy in such cases.

CHAPTER

8 SYSTEMIC THERAPY

Some form of systemic therapy with either hormone therapy, chemotherapy or targeted therapy in various combination and sequences is offered to almost all breast cancer patients. The choice of systemic therapy and combination of systemic therapy used in modern practice is based on large RCTs consisting of several thousand patients and meta-analysis and is outlined here.

Systemic Therapy (Levels of Evidence in Parentheses) in OBC/ LOBC/LABC



*Six cycles of an anthracycline regimen (FEC-90-100 or FAC) is a standard regimen in node negative patients. Taxanes may be added in some high risk patients (high grade, triple negative or HER2 positive). CMF is an option in some patients with cardiac risk and/or some elderly women[34].The benefit of adjuvant chemotherapy in node negative breast cancer, both in premenopausal and postmenopausal patients has been established in large EBCTCG meta analyses. A number of risk stratification schemes such as the St Gallen's[5] and Adjuvant Online! can be used to decide adjuvant chemotherapy. A number of tests using multigene classifiers such as Recurrence Score and Mamma print are available but are yet to be validated in prospective randomized studies and are expensive. Therefore their routine use for decision making is not recommended. Recently IHC4 test (ER, PR, HER2 &Ki-67) has been shown to provide similar information. However standardization of Ki-67 is a matter of concern for its routine use.

**Patients with small (<2cm), node negative, ER or PR positive, HER2 negative, low grade tumors may be considered for adjuvant endocrine therapy alone[5]. Performance of a locally standardized marker of proliferation such as Ki-67 can further aid in selecting low proliferative tumors in whom chemotherapy may be avoided.

***Six to eight cycles of a standard anthracycline-taxane regimen (AC/EC-paclitaxel/docetaxel, FEC-docetaxel, TAC, etc) is standard adjuvant chemotherapy for node positive breast cancer. Consider weekly or every 2-week scheduling for paclitaxel and every 3 week scheduling for docetaxel.[35] Docetaxel

based chemotherapy and dose dense anthracycline/paclitaxel (2 weekly) based chemotherapy should be supported with prophylactic G-CSF support.

****Anthracycline and taxane regimens are standard NACT regimens in LABC. Surgery can be sandwiched between pre- and post-operative chemotherapy or in responding tumours, all chemotherapy can be pre-operative, as per institutional practice.

*****Tamoxifen for five years in pre-menopausal women is standard adjuvant endocrine therapy. Aromatase inhibitor (AI) containing regimens (Tam-AI switch or 5 years of AI) constitute standard adjuvant endocrine therapy in post-menopausal patients. The ATLAS trial has now established the role of tamoxifen beyond 5 years and this option should be offered to those with high recurrence risk (Lancet. 2013;381:805–816). Consider extended adjuvant therapy with letrozole after 5 years of tamoxifen in node positive post-menopausal women. Tamoxifen for 5 years is an acceptable alternative in post-menopausal women[36,37].

******Adjuvant trastuzumab, if feasible, improves outcome in patients with HER2 positive non-metastatic breast cancer. As most trials have used it for 1year, this duration is considered standard as per current international guidelines. However, one small trial that used adjuvant trastuzumab for 9 weeks also showed a trend towards improved outcome. Therefore 9-12 weeks of adjuvant trastuzumab preferably given with concurrent taxane followed by 4 cycles of anthracycline based regimen can also be considered an acceptable alternative. Addition of trastuzumab to neoadjuvant chemotherapy should be considered in view of improved outcome in randomized trials[38-40]. When not feasible, the use of chemotherapy (preferably anthracycline based) without traztuzumab is an acceptable alternative in patients with HER2 over-expressing tumors.

CHAPTER

9 RADIOTHERAPY

Postoperative RT using Linac or telecobalt to the breast/ chest wall with or without lymphatic areas is indicated in most cases, except after mastectomy for a DCIS or early node negative cancer. Several large RCTs have shown that post mastectomy radiotherapy in women with T3-4, N+ cancers, improve loco-regional control as well as survival[41,42] Large randomized trials have also shown that radiotherapy after conservative surgery is integral in achieving loco-regional control comparable to mastectomy and with improved body image[43,44] . The aim is to use an appropriate technique for safely giving adequate doses of radiation, equivalent to 50Gy/25#/5weeks, to control subclinical disease in tissues at risk (chest wall/ breast+/-SCF).

A. Indications for postoperative Radiotherapy

Post Mastectomy RT (PMRT) to chest wall +/- nodal area

- >3 axillary nodes positive
- Any number of nodes positive after NACT
- Clinically or Pathologically T3 or T4 Tumour
- Positive resection margins
- Known residual disease in axilla
- Initial involvement of SCF/IMC
- For 1-3 nodes +ve, PMRT is being increasingly considered following recent EBCTCG metaanalysis (McGale et al. Lancet. 2014), which showed improvement in breast cancer specific mortality. With routine use of more effective chemotherapy, the absolute benefit of PMRT in patients with 1-3 node +ve but smaller tumours with favourable features is likely to be less and may be individualized based on age and comorbidity.

After Breast Conservative Surgery: All cases of BCT require postoperative RT. However, RT may be avoided in selected elderly women with small, node –ve, low grade, ER/PR+ve tumours with low risk of recurrence as seen in the recent PRIME trial (Kunkler et al Lancet Oncology, 2015)

IMC RT: RT to IMC fell into disuse after its associated excess cardiac mortality became evident. Two recent RCTs - EORTC (Poortman et al, NEJM 2015) and MA-20 (Whelan et al, NEJM 2015) evaluating the role of RT to SCF plus IMC in patients with medial or central quadrant tumours or those with axillary node +ve, showed a modest improvement in DFS but no difference in overall survival. Moreover, the contribution of IMC RT in the very modest benefit with SCF plus IMC RT is likely to be even smaller. In addition there are technical challenges in planning and delivering cardiac safe IMC RT. Hence most centres around the world continue to offer IMC RT only for cases with radiological or pathological evidence of IMC node involvement.

Axilla: It is a common practice in many Indian centres to treat axilla for all node +ve cases, possibly due to sub-optimal axillary surgery or histopathological evaluation in practice settings. As post-op axillary RT can increase arm & shoulder morbidity, it is advocated for residual axillary disease or node +ve after inadequate axillary surgery and revision surgery is not being considered for various reasons. Recently the EORTC-AMAROS trial (Donker et al, Lancet Oncol. 2014) shows that in T1-2 clinically node negative with sentinel node biopsy +ve, axillary RT results in excellent disease control comparable to completion axillary dissection but with different morbidity pattern.

B. Treatment Area and Technique for Radiotherapy

1. Chest wall: Bitangential portals, isocentric or with breast cone. Bolus if skin was involved or at high risk of recurrence. For left sided tumours, minimize cardiac dose with appropriate beam angulation and cardiac shielding if required.

2. Whole Breast: Bitangential portals; Isocentric, with appropriate wedges. 3DCRT or IMRT if large breasts to reduce acute/late toxicity in areas of dose inhomogeneity. LINAC preferable but Telecobalt can be used if Interfiled separation is <18cm & breast is not large. Avoid cardiac dose with beam placement or cardiac shielding.

3. SCF (in axillary N+ cases or initial SCF involvement): Direct anterior portals, avoiding overlap with tangents to prevent matchline fibrosis and rare occurrence of brachial plexopathy.

4. Axilla: When indicated, axilla can be irradiated with an anterior extended SCF field with posterior axillary boost.

5. IMC (in known IMC involvement): CT planned partially wide tangents or mixed electron/photon ports on LINAC.

6. Tumor Bed boost (In all cases of BCT except for DCIS and in postmenopausal women with small tumors with favorable histology and-ve margins): Enface electrons, 3D CRT or in selected cases, HDR brachytherapy in expert centres.

C. Radiotherapy dose and fractionation

50Gy in 25 daily fractions over 5 weeks or its equivalent hypofractionated regime of 40Gy/15 fractions over 3 weeks or 42.5Gy/16# over 3 weeks[45,46]. Hypofractionated regimen is equivalent to the conventional regimen in terms of disease control and survival. These hypofractionated regimens results in significantly lower incidence of acute and late breast toxicity and without excess cardiac morbidity at 15 year. The 3 week hypofractionated regime has become the standard of care in the UK, Canada and many large volume Indian centres for BCT and post mastectomy RT. For hypofractionated regimes, appropriate planning should be done to minimize dose inhomogeneity and cardiac dose. **Tumor Bed Boost** after whole breast RT for BCT is given with appropriate energy electrons or 3DCRT photons to a dose of 10–16Gy with 2-2.5 Gy per fraction. For HDR boost a twice daily regimen of 4.5 - 5 Gy x 2 or 3.4Gy x 3 fractions.

D. Accelerated partial breast radiation (APBI)

This short and convenient course of RT has been tested in several large RCTs which are yet to report long-term results. Hence it should be considered an investigational approach. Currently, centres with experience are offering APBI to carefully select postmenopausal women with node negative, small tumors with clear margins and no adverse pathological features[47]. A recent European RCT compared multicatheter interstitial APBI with whole breast RT + boost in 1184 women >40 years of age with up to 3 cm tumour, pNo or pNmi. It shows equivalent disease control and survival at a median follow up of 6.6 years (Strnad et al, Lancet, 2015) and this was evident in all age groups above 40 years and in all tumor types.

E. Palliative Radiotherapy is described in the chapter of metastatic disease.

CHAPTER

10 FOLLOW UP

Patients and their families should be counseled on the need for regular follow up in order to

1. Timely detection and salvage of loco-regional recurrences
2. Timely detection and treatment of contralateral breast caner
3. Detect and treat metastatic disease when symptomatic and prevent its complications.
4. Monitor and manage any late sequelae of treatment including those of treatment induced menopause.
5. Address any quality of life and survivorship issues arising in subsequent years.

At follow up visits take detailed history, especially of any metastatic symptoms or physical or psycho-social sequelae of treatment or menopausal symptoms. Clinical examination is complemented with mammogram (bilateral if BCT has been done) every 12 – 24 months. Randomized trials[48,49] have shown that regular follow up laboratory or radiological investigations does not improve survival or quality of life hence they are not recommended.

The follow-up frequency suggested in the first 5 years is every 6 months or earlier if any symptoms. Subsequent visits could be annual up to10 years and then 2 yearly.

Patients with significant family history of cancer or known BRCA mutation should be kept on lifelong 6 monthly or annual follow up as they have a much higher risk of contralateral breast cancer and ovarian cancer. Cancer screening and prevention strategies for these women is described later.

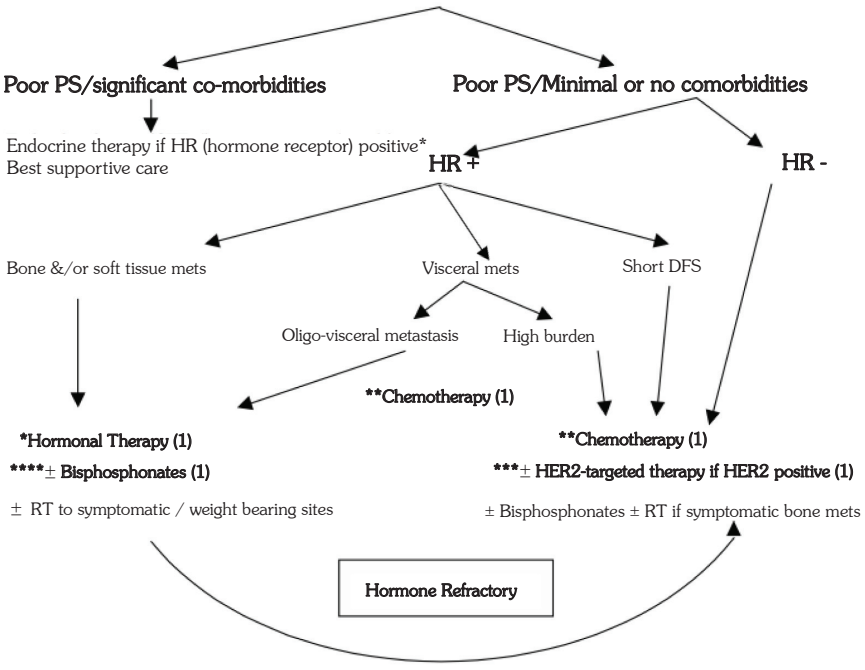
CHAPTER

11 METASTATIC BREAST CANCER

The metastatic disease may be symptomatic or asymptomatic and detected at initial presentation or during follow up. The overarching goal of managing metastatic breast cancer is to allow the patient to regain and maintain the best possible quality of life and to prolong her life to the extent possible. This requires careful assessment and documentation of cancer associated symptoms, previous treatment history along with the nature, extent and tempo of loco-regional and metastatic disease. In addition to assessing prognostic and predictive factors like ER/PR and HER2neu, patient's physiological, psychological and financial reserve and support system should also be assessed. This helps in providing individualized holistic care which could range from intensive chemotherapy to only best supportive care, in consultation with the patient and the family. As most Indian centres do not have a specialized palliative care unit, the treating oncologist will be required to provide symptom control including pain control using pharmacological and non-pharmacological approaches.

11.1 Management algorithm (Levels of Evidence in Parentheses)

Detailed History and physical examination including Performance Status (PS) and co-morbidities along with routine blood tests and imaging (plain radiographs, ultrasound, CT scan, bone scan, PET-CT scan) is done as appropriate



Document the site and extent of metastatic disease and loco-regional disease if any. Measurable lesions should be specifically documented for response assessment.

Initiate counseling, pain control, medication and symptom control measures as required. Early referral to palliative care unit is desirable.

NOTES

*Hormonal Therapy[50,51,58]

- Premenopausal–Tamoxifen. On progression consider ovarian suppression followed by aromatase inhibitors (AI).
- Postmenopausal - Aromatase inhibitor or Tamoxifen. On progression, tamoxifen, fulvestrant or other AI.

**Chemotherapy[52-55,58]

- Combination chemotherapy is preferred in patients with high visceral burden and in other cases single agents can be used.
- Longer duration of chemotherapy for metastatic breast cancer is associated with modest improvement in overall and progression free survival. Chemotherapy duration should be individualized.
- Anthracyclines or taxanes are the preferred first line agents if they have not been used earlier. In anthracycline and taxane pretreated patients consider capecitabine, platinum, rechallenge with taxanes including nano paclitaxel versions, vinorelbine, gemcitabine and ixabepilone.

***HER2 Targeted therapy[56,58]

- In HER2 positive patients consider trastuzumab, lapatinib or their combination in addition to chemotherapy if it is feasible.

****Bisphosphonates[57,58]

- Patients with bone metastases should be considered for regular intravenous bisphosphonates like zoledronic acid 4mg every 4 weeks with RFT monitoring.

Mastectomy

In patients with metastatic disease, mastectomy is considered for palliation of symptoms such as fungation or bleeding, especially when locoregional disease is progressing on systemic therapy and is still resectable with primary skin closure. For patients with isolated or few metastasis (oligo-metastasis), role of definitive loco-regional treatment is uncertain. A recent Indian RCT has shown that locoregional treatment in such patients does not improve survival (Badwe et al. Lancet Oncology, 2015).

Palliative Care

In patients with metastatic disease, the patient should be referred to the palliative care unit or pain clinic at the earliest. Not only this helps to achieve prompt symptom control but the quality of life is better maintained with holistic care. If a specialized palliative care unit is not accessible, the treating oncologist should provide comprehensive care and symptom control including pain control. Availability of morphine is still an issue in some parts of the country.

Palliative Radiotherapy

Bone metastasis

Radiotherapy along with Bisphosponates is the main stay of treatment for symptomatic bone metastasis.

For isolated or few bone metastases, the affected bones with some margins is irradiated with 8Gy single fraction at the earliest possible opportunity[59].

Fractionated radiotherapy of 20Gy/5# or 30Gy/10# should be considered in patients with impending fracture or cord compression[60] Established fractures in patients with at least few months of life expectancy should be fixed surgically and then given postoperative RT. For patients with widely disseminated and symptomatic bone metastasis in whom chemotherapy is not indicated immediately, Hemi Body Irradiation (HBI) as single dose of 6Gy Upper HBI or 8Gy Lower HBI, produces excellent symptom relief [61]. If both Upper and Lower HBI are required, the more symptomatic half should be treated first and a gap of 4-6 weeks should be maintained to allow the marrow to recover. After HBI, chemotherapy should be deferred for 4-6 weeks or longer to prevent severe myelosuppression. Upper HBI should be avoided in patients with compromised lung function.

Brain metastasis

Most symptomatic patients would benefit from steroids and fractionated Whole brain RT (WBRT)[62]. Recommended dose is 20Gy/5#/1week or 30Gy/10#/2weeks. The MRC trial had shown that in patients with poor GC and widely disseminated disease, 12Gy in 2 fractions on consecutive days (or 1 week apart) is comparable to 30Gy/10#/2 weeks (Priestman et al, Clin. Oncology, 1996).

For single brain metastasis in patients with controlled primary and no other site of systemic disease, consider surgery or radiosurgery of the brain lesion followed by whole brain radiotherapy. Recent NCCTG trial (ASCO 2015) shows that in patients with 1-3 brain metastases, addition of WBRT to SRS improved intracranial control without improving survival and with adverse impact on cognitive function. SRS alone should be judiciously used in highly select patients.

Spinal cord compression

Palliative Radiotherapy (20Gy/5# or 30Gy/10#) with steroids is the mainstay of treatment. Select cases with life expectancy of more than 6 months presenting with recent onset paraparesis or paraplegia and limited vertebral involvement should be considered for surgical decompression prior to palliative radiotherapy.

CHAPTER

12 HEREDITARY BREAST CANCER

Hereditary cancer accounts for 5% of all breast cancers and a greater proportion of ovarian cancers. Germline mutations in two breast cancer susceptibility genes BRCA1 and BRCA2 account for over 50% of the Hereditary Breast Ovarian Cancer (HBOC) families. Mutation in TP53 gene accounts for a small fraction of families, as part of Li-Fraumeni syndrome.

Clinico-pathological features of hereditary breast cancer

- Younger age at diagnosis (1-2 decade earlier)
- Greater propensity for multi-focal involvement
- High probability (50%) for synchronous or metachronous bilateral breast cancer
- BRCA1 associated breast cancers have a distinct genetic signature of Basal Type with preponderance of poorly differentiated ER, PR and HER2-ve (Triple negative) tumours.

A genetic risk assessment and referral for genetics evaluation should be considered in:

- Early onset breast or ovarian cancer, especially if it is triple negative breast cancer
- Personal history of bilateral breast, or bilateral ovarian cancers.
- Personal history of primary breast and ovarian cancer in the same individual.
- Personal history of breast or ovarian cancer, along with family history of one or more family members with breast, ovarian or some other cancer.
- A known BRCA1 or BRCA2 mutation in a blood relative.
- Member of an ethnic community with known founder BRCA1/2 mutation.
- Any women concerned about her hereditary cancer risk

Genetic Testing using BRCA1/2 gene sequencing recommended for women with strong family history of early onset breast and or ovarian cancer or when the calculated probability of finding a BRCA mutation is >10%[8].

There are very limited centres for comprehensive genetic counseling, genetic testing and medical management of carriers in India. One such centre is the **ICMR** Centre for Advanced Research in Cancer Genetics at ACTREC, Tata Memorial Centre in Mumbai (cgc@actrec.gov.in).

Screening for women from HBOC families or known BRCA mutation carriers should start at the age of 25 years or 5 years before the youngest affected member in that family, whichever is earlier.

- Monthly breast self examination
- Six monthly clinical breast examination

- Annual breast imaging. Due to dense breasts in these young women, clinical examination, mammography and ultrasound all have poor sensitivity. In experienced centres, MRI has much higher sensitivity for detecting breast cancer in such women[2].
- With no clear benefit of ovarian cancer screening with Transvaginal USG and CA-125, it is not routinely recommended.

Cancer Prevention: The options for cancer prevention in these high-risk women include chemoprevention using tomoxifen; Risk Reducing Salpingo-Oopherectomy (RRSO) and Bilateral Prophylactic Mastectomy (BPM) with reconstruction. The final decision regarding the procedure undertaken is made jointly after taking into consideration the patient's wishes after providing full information regarding the pros and cons of the procedure. The most useful prophylactic procedure is RRSO, at the age of 35-40 years and after completion of child bearing[63]. This reduces the risk of ovarian cancer by 99% and of breast cancer by 50%.

Clinical trials of Platinum agents and PARP inhibitors are underway for women with *BRCA1/2* associated hereditary breast or ovarian cancer.

CHAPTER

13 RESEARCH ISSUES

1. Risk factors for breast cancer in Indian women in the context of changing life styles
2. Behaviour of breast cancer in young women as relevant to Indian demography
3. Pragmatic and effective population based screening programmes
4. Opportunistic or targeted screening for high risk or concerned women
5. Standardization and improving quality of radiological, cytological and histopathological diagnosis and staging of breast cancer.
6. Safety and efficacy of breast conserving surgery in LABC
7. Sentinel node biopsy and axillary sampling
8. Novel techniques and fractionation of radiotherapy to improve cost effectiveness and throughput
9. Role of PET-CT in staging and response assessment
10. Pragmatic and cost effective approaches like primary progesterone
11. Developing strategies for genetic testing, counselling and risk management for hereditary breast cancer
12. Role of targeted therapies
13. Genomic characterization of breast cancer in Indian women